

Cleveland Clinic Quarterly

Published by
The Staff of the Cleveland Clinic
CLEVELAND, OHIO

CONTENTS

	<i>Page</i>
FURTHER EXPERIENCE WITH ANTICHOLINERGIC DRUGS: A CLINICAL APPRAISAL IN 201 PATIENTS	
	<i>Charles H. Brown, M.D.</i> 415
VITAMIN A INTOXICATION	
	<i>Mary T. Harrison, M.D. and Robert D. Mercer, M.D.</i> 424
RESPONSES TO CORTICOTROPIN (ACTH) AND CORTISONE IN THROMBOCYTOPENIC STATES	
	<i>James S. Hewlett, M.D. and Thornton Scott, M.D.</i> 430
LENS IN ANTERIOR OF EYE: SURGICAL REMOVAL	
	<i>Robert L. Alexander, M.D. and Roscoe J. Kennedy, M.D.</i> 437
END RESULTS IN RETINAL DETACHMENT SURGERY	
	<i>Roscoe J. Kennedy, M.D. and Philip Kazdan, M.D.</i> 441
MUCOEPIDERMOID CARCINOMA OF SALIVARY GLAND ORIGIN	
	<i>George F. Stevenson, M.D. and John B. Hazard, M.D.</i> 445
EQUIPMENT FOR SAFE HANDLING OF RADIOACTIVE ISOTOPES	
	<i>Otto Glasser, Ph.D. and Bernard Tautkins</i> 457

BUNTS INSTITUTE

PUBLICATIONS	463
ANNOUNCEMENTS	
Physician-in-Chief Pro Tempore	
Saturday Morning Teaching Program	464
POSTGRADUATE COURSE	
Refresher Course in General Surgery, October 28 and 29, 1953	465
INDEX—Volume 20—1953	469

OCTOBER, 1953

Volume 20

Number 4

CLEVELAND CLINIC QUARTERLY

EDITORIAL BOARD

John B. Hazard, M.D., Editor

William J. Engel, M.D.

A. Carlton Ernstene, M.D.

A. C. Corcoran, M.D.

Fay A. LeFevre, M.D.

MANUSCRIPT EDITOR Patricia Virostko

MEDICAL ARTIST C. Kurt Smolen

MEDICAL PHOTOGRAPHER Thomas J. Lannon

Issued in four numbers during the year, one in January, one in April, one in July and one in October by Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland 6, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office at Cleveland, Ohio, under the act of August 24, 1912.

Copyright, 1953, by The Cleveland Clinic Foundation

FURTHER EXPERIENCE WITH ANTICHOLINERGIC DRUGS:

A Clinical Appraisal in 201 Patients

CHARLES H. BROWN, M.D.

Department of Gastroenterology

THE formation of a peptic ulcer is associated with the action of acid peptic juice. When free hydrochloric acid is absent, its formation is impossible. Conversely, increased free acid secretion is commonly present in patients with duodenal ulcer. Although the ancient Greeks and Romans used alkalies for the treatment of "acid stomach," Sippy¹ was the first to introduce an intensive program of neutralizing the gastric acidity in patients with peptic ulcer. His treatment resulted in a high percentage of healing. Various modifications of Sippy's original treatment using different neutralizing agents and a more liberal diet have appeared, but the basis for the treatment of peptic ulcer—adequate neutralization of gastric acidity—has remained the same.

The physiologic basis for the operations of vagotomy and gastroenterostomy for duodenal ulcer is the fact that patients with these ulcers have increased acidity and secretion^{2,3} due to vagal stimulation which can be abolished by section of the vagal nerves to the stomach.^{4,5} Since cutting the vagus nerves decreases acidity and secretion, the possibility of medically blocking the vagal impulses as treatment for duodenal ulcer arose. The Sippy program is one of neutralizing the excess acid secreted. The objective of anticholinergic drugs is to suppress and prevent the excess acid secretion.

Tetraethyl ammonium chloride is capable of decreasing gastric secretion and motility and is an effective drug for this purpose. However, it must be given intravenously, the action is relatively brief, and it causes extreme hypotension. The hexamethonium salts are blocking agents, but again have a generalized action that results in prolonged hypotension. The effect of the hexamethonium salts on gastric secretion has been sufficient to cause the British to use them in the treatment of duodenal ulcer, but the hypotension produced made the drug impractical for this purpose. Atropine and belladonna have been used for years but their effect on gastric secretion and motility is minimal even though large doses are given which cause excessive dryness and loss of accommodation.

An anticholinergic drug, Banthine, was made available to us in January 1950 for clinical trial. Longino et al.⁶ reported that this drug caused prolonged depression of gastrointestinal motility and usually reduction in volume and acidity of gastric secretions. Smith et al.⁷ found that Banthine produced a "marked reduction in the secretion of gastric juice in dogs" and a "marked reduction in the nocturnal gastric secretions of peptic ulcer patients."

Banthine was given to 117 of our patients with duodenal ulcer.^{8,9} Most of the patients were not given antacids or other medications in order to evaluate the effect of the drug itself. Ninety-seven of 117 patients experienced prompt relief that usually occurred within two to three days. Progress roentgen examinations of the stomach were obtained for 69 patients; the crater disappeared in 55 patients and became smaller in five. The symptomatic and roentgenologic responses of these patients suggest that anticholinergic drugs may have an extremely useful function in the treatment of duodenal ulcer.

Kirsner and Palmer,¹⁰ studying the effect of 16 new anticholinergic drugs in producing anacidity, found that Pamine, Win 4369, and Probanthine were the most potent after intragastric administration; partially effective anti-secretory drugs included Antrenyl and Prantal. They stated, "None of the currently available anti-secretory drugs consistently produces an anacidity in man without side effects."

Sleisenger, Eisenbud, and Almy¹¹ compared the effectiveness of 18 antispasmodic drugs on colon motility as determined by balloon studies. Among the drugs that we have used, they found that Bentyl was variably effective, and that Probanthine, Prantal, and Antrenyl were frequently effective. They found a close correlation between side effects and effectiveness on colonic motility, and suggested that "any anticholinergic drug which clinically has no side effects, probably has no action upon the colon." There have been many other reports on the pharmacology and physiology of these new anticholinergic drugs; it is not our purpose to review these studies.

Because of the results that we obtained with Banthine in 1950, we have been interested in other anticholinergic drugs that might have fewer side reactions and a more specific action on gastric motility and secretion. The purpose of this report is to review our clinical appraisal of some of the new anticholinergic drugs in 201 patients.

RESULTS

Since the introduction of Banthine, a large number of similar and related compounds have been introduced. It has not been possible to study all of them, but we have tried to evaluate clinically a few of the most promising. Since Banthine was an entirely new type of treatment for duodenal ulcer, and since early results appeared promising, we withheld antacids and frequent feedings to evaluate the drug more accurately. Since anticholinergic therapy has already been shown by us and others to be helpful, we did not feel justified in withholding antacids and frequent feedings merely to ascertain the relative merits of different anticholinergic drugs. Because the combination of antacid therapy and frequent feedings¹² is usually an extremely effective treatment of duodenal ulcer, it becomes difficult to evaluate a drug that is added to other treatment. Therefore, realizing these shortcomings, our results are presented as clinical impressions and not as the findings from controlled experiments.

1. **Pamine (UO-382)*** was supplied to us in 5 mg. tablets (now available in 2.5 mg. tablets). McHardy et al.¹³ obtained complete symptomatic relief in 16 and partial relief in 3 of a total of 20 patients given this drug without antacid therapy. Progress x-rays showed the ulcer completely healed in ten, the crater disappeared in four, residual irritability in four, and no change in two.

This medication was given to 40 patients, 34 of whom had duodenal ulcer and 6 of whom had other gastrointestinal conditions. Five patients were given 10 mg. q.i.d. Only one patient of the five tolerated this dose, and he complained of dryness of the mouth. The dose was reduced to 1 tablet (5 mg.) q.i.d. in the four other patients, because they complained of dryness, lack of accommodation, hoarseness and urinary symptoms.

Thirty-nine patients were then given 1 tablet (5 mg.) q.i.d. or 20 mg. a day. Four patients did not tolerate this dose, all had excessive dryness, one had lack of accommodation, one urinary distress and one nausea. Nineteen had some side reactions (dryness in 16, lack of accommodation in 4, and slowness of the urinary stream in 2), but they were able to continue the full dose. Sixteen of the 40 patients had no side effects.

Sixteen patients with duodenal ulcer were given a trial on Pamine alone without any antacids or diet for one to two weeks. Fifteen of the 16 patients obtained complete and one partial relief of their ulcer symptoms. Pamine administration to 18 other patients with duodenal ulcer was supplemented with an hour ulcer schedule,¹² and all obtained complete relief. Progress roentgen examinations were obtained in 15 of the 34 patients and showed that the ulcer crater had disappeared in 11, was smaller in 3, and in 1 patient there was less deformity.

Six patients with other gastrointestinal conditions were given Pamine in the same dosage. Of two patients with ulcerative colitis, one had less diarrhea and the other noted no effect. The drug was helpful to one patient with "hyperacidity syndrome" but not to another. One patient with severe chronic pancreatitis obtained relief, but the side effects were too severe. The sixth patient also did not tolerate the drug.

Our experience suggests that Pamine in a dose of 5 mg. q.i.d. is of considerable help to the patient with a duodenal ulcer, but is of less value in other gastrointestinal conditions. Ten per cent of the patients did not tolerate this dosage, and almost half had minor side reactions but were able to continue with the medication. Five mg. q.i.d. should be an effective dose.

2. **Probanthine (SC-3171)**** was supplied to us in large white tablets of 15 mg. each. It is now on the market in smaller pink tablets of the same dose. A total of 64 patients were given Probanthine. Twenty-three were given a dose of two tablets or 30 mg. q.i.d. which was reduced in five patients because of side effects of dryness, loss of accommodation, slow urination and constipation. Six other patients had similar side reactions which were not too severe and they were able to maintain this dose. Twelve patients had no side reactions.

The remaining 41 patients and the 5 for whom a dose reduction was

*Kindly supplied by Dr. Joseph P. Webb of the Upjohn Company.

**We are indebted to Dr. Irwin C. Winter of G. D. Searle and Co. for supplying the Probanthine.

necessary were given 15 mg. q.i.d. The medication was stopped for three patients, one because of urinary difficulty and two because of increased stomach distress. Of the remaining 43 patients, 38 had no appreciable side reaction, while 5 complained of some dryness and urinary difficulty, but were able to continue with the full dose.

Of the 64 patients given Probanthine, 40 were patients with duodenal ulcer. Eight patients were given Probanthine alone without antacids and interval feedings for a short time, and seven obtained relief on Probanthine alone. Thirty-two patients were given this drug in addition to the regular ulcer schedule;¹² 30 of these improved symptomatically, while 2 thought the medication made their gastric symptoms worse. Progress roentgen examination in 21 patients showed the ulcer crater had disappeared in 16, was smaller in 2, had persisted in 2, and in 1 patient there was less deformity.

Probanthine was used in 24 patients with other conditions. It relieved eight of ten patients with "hyperacidity syndrome" but without a demonstrable ulcer. It was helpful to one patient with hypermotility and decreased the ileal discharges in one patient with an ileostomy. One patient with regional enteritis noted less diarrhea, but two patients with chronic ulcerative colitis and one with extensive lymphosarcoma of the small intestine noted no change. Four patients with irritable colon, one with dysmenorrhea, one with chronic pancreatitis, and two with dumping syndrome, thought the drug was helpful. It was of questionable value to one patient with gastric crises.

The preceding results suggest that Probanthine may be a useful adjunct in the treatment of duodenal ulcer and some other gastrointestinal conditions. Eighteen of 23 patients tolerated 30 mg. q.i.d., and only minimal side reactions were noted with 1 tablet or 15 mg. q.i.d. Six to eight tablets daily should be an effective dose with minimal side reactions for most patients.

3. Prantal* was originally supplied in 50 mg. tablets. A dose of 50 mg. q.i.d. proved ineffectual, and the size of the tablets was increased to 100 mg. Sixty patients were given Prantal. Five patients tolerated two tablets or 200 mg. q.i.d. without serious side effects. The remaining 55 patients tolerated 100 mg. q.i.d. with minimal reactions. The drug had to be stopped in only four patients because of excessive dryness in two, slowness of urination in two, and increased gas and bloating and "choking" in one each. Six other patients complained of minimal side reactions consisting of the same symptoms, but were able to continue with the medication.

Of the 60 patients given Prantal, 50 had duodenal ulcers. Only 3 of these 50 were given the drug alone without antacids, but they all obtained relief. Three patients obtained no relief on both Prantal and an hour ulcer schedule, and all required surgery; the duodenal ulcer perforated in one of the three patients while he was on Prantal. Four patients obtained only partial relief on both Prantal and routine ulcer management, and all believed Banthine was

*Kindly supplied by Dr. Edward Henderson, the Schering Corp. Most of the patients given Prantal were treated by E. N. Collins, M.D., J. A. Ecker, M.D. and H. S. Bennett, M.D. of the Department of Gastroenterology. We are grateful to them for permission to include these patients in this report.

more effective. The remaining 40 patients obtained relief on both Prantal and the intensive ulcer schedule.¹² Progress roentgen examinations were obtained in 37 patients, and showed the ulcer crater had healed in 23, was smaller in 4, and had persisted in 7. In three patients there was less deformity. The crater had not healed in two months in 11 of the 37 patients in whom we were able to obtain progress x-rays.

Prantal was given to ten patients with other gastrointestinal conditions, and was helpful in four of five patients with "hyperacidity syndrome," one with hypersalivation, and in one patient with ulcerative colitis. It was of no aid to one patient with an irritable colon, one with hypersalivation, and one with a severe gastric neurosis.

Only three patients were given Prantal alone without antacids or other treatment, so that evaluation of the drug is difficult. The drug caused few side reactions and was well tolerated in a dose of 100 mg. q.i.d. We did not feel it was as effective in the dosage used as were Pamine or Probanthine. Three patients required surgery despite Prantal, and the ulcer persisted in 11 of 37 patients who had progress roentgenograms. Possibly a greater dose (i.e. 200 mg. q.i.d.) would be more effective.

4. Antrenyl* was supplied in 5 mg. tablets. Eight patients (seven with duodenal ulcer) were given this drug. Seven patients tolerated 4 tablets q.i.d. while one patient tolerated 2 tablets q.i.d.

Six of the seven patients with duodenal ulcers obtained relief, four on Antrenyl alone and two on Antrenyl plus antacid therapy. The seventh patient who had a penetrating ulcer did not obtain relief and required surgical intervention. The ulcer crater disappeared in two months in the six patients who continued medical treatment. One patient with a hiatus hernia and short esophagus, who also required surgery, discontinued Antrenyl because of increased nausea.

This is a very small series, but suggests that Antrenyl may be a useful anticholinergic drug. It partially corroborates the report of Rogers and Gray¹⁴ who found a favorable response to Antrenyl alone in 24 patients with duodenal ulcer.

5. Win 4369** was supplied in tablets of 5 mg. Of nine patients given the drug, three tolerated 6 tablets a day, while six tolerated 4 tablets a day. Three patients with duodenal ulcer obtained relief, two on Win 4369 alone. The crater disappeared in two patients for whom progress roentgenograms were obtained. Two patients with irritable colon, one with regional enteritis and one with ulcerative colitis noted some improvement on the drug. One patient with unexplained diarrhea and one with ulcerative colitis had no decrease in diarrhea. There are suggestions in the few patients studied that Win 4369 may be a useful anticholinergic drug.

6. Bentyl†, 10 mg. capsules, was used in 20 patients. We could observe

*Kindly supplied by Dr. J. H. Walton of the Ciba Company.

**Kindly supplied by Dr. W. A. Curran of the Winthrop-Stearns Company.

†Kindly supplied by Dr. R. C. Pogge of the Wm. S. Merrill Company.

no effect in eight patients with duodenal ulcer who were given this drug for short periods, so we discontinued its use in these patients. Seven patients with irritable colon syndrome obtained some relief on the medication, and felt it was better than tincture of belladonna. Chamberlin¹⁵ and Collins¹⁶ have believed it to be helpful in some patients with irritable colon. It appeared to us that this drug was relatively impotent in patients with duodenal ulcer, but may be of some value in patients with irritable colon syndrome. We believe, however, that more potent antispasmodic drugs are available.

DISCUSSION

A number of new anticholinergic drugs have been used clinically and appear to be effective and important adjuncts in the treatment of duodenal ulcer. Pamine seemed to be the most effective in a dose of 5 mg. q.i.d., but was associated with minimal side reactions in more than half of the patients. Results with Probanthine were almost as satisfactory, and patients on this drug had fewer side reactions than those on Pamine. Fifteen of 16 patients with duodenal ulcer on Pamine alone and seven of eight patients on Probanthine alone obtained symptomatic relief. Although fewer side reactions were obtained with Prantal in a dose of 100 mg. q.i.d., the results were less favorable than those obtained with Pamine and Probanthine for the ulcer crater persisted in 11 of 37 patients treated with Prantal. Antrenyl and Win 4369 showed promise, but they were used in only eight and nine patients, respectively. We could see no particular benefit from Bentyt.

The newer anticholinergic drugs studied seemed to cause fewer side reactions than Banthine, and they did not have the bitter taste of Banthine. No serious reactions were observed. The side reactions noted were similar to those caused by Banthine, and consisted of excessive dryness of the mouth, lack of accommodation, hoarseness, difficulty in urination with slowness of the urinary stream, and constipation. Occasionally a patient complained of some decrease in libido. The drugs rarely caused an increase in the patient's symptoms with more gas and bloating.

Dose. The dose of the anticholinergic drug that is effective in decreasing gastric acid secretion and motility may be the same dose that causes minimal side effects. We believe, therefore, that the proper dosage for each patient must be individualized. Only by causing minimal side effects can one be sure the patient is getting a dose adequate to decrease acid secretion and motility. We believe adequate dosage is most important, and our poorer results with Prantal may have been due to an inadequate dose of the drug. Suggested doses that one should strive for with these drugs are: Pamine—5 mg. or two tablets q.i.d., Probanthine—30 mg. or two tablets q.i.d., Prantal—200 mg. or two tablets q.i.d. All patients will not tolerate these doses, and the number of tablets taken daily may have to be decreased. It must be remembered also that some patients can tolerate a greater dose after they have received the medication for one to two weeks, than they can at the onset of treatment.

Contraindications. The contraindications to other anticholinergic drugs

are the same as those to Banthine, namely: (1) Bladder neck obstruction. We have seen several patients develop acute urinary retention with these medicines. Due to a decrease of bladder motility and tone, these drugs can convert a partial bladder neck obstruction into a complete acute obstruction. (2) Coronary insufficiency and cardiac decompensation. These drugs increase the heart rate, and so may increase the frequency of anginal attacks in patients with coronary insufficiency. A physician-patient of mine noted a definite increase in the frequency of his anginal attacks whenever he attempted to take any of these medications for a penetrating ulcer. Under proper supervision, many cardiac patients may tolerate the medication. (3) Glaucoma. These medications cause changes in accommodation. (4) Achalasia and (5) Pyloric obstruction. These drugs decrease gastrointestinal motility and should not be used in such cases until the obstruction is relieved by other measures.

Indications

Ulcer. The chief indication for anticholinergic drugs is duodenal ulcer. While withholding antacids and using these drugs alone is helpful in evaluating the medicine, we do not advise such a practice in the routine treatment of patients. The antacid therapy of peptic ulcer is well founded and is effective. We believe that the best treatment for an active ulcer is a combination of an intensive hour ulcer schedule as outlined elsewhere¹² and anticholinergic drugs. Anticholinergic therapy will not eliminate the necessity for surgery in patients with complicated duodenal ulcer, such as organic obstruction, perforation and repeated hemorrhage, but their use with conventional treatment has in our hands considerably decreased the number of patients referred to the surgeons. Anticholinergic drugs do not replace adequate medical treatment for duodenal ulcer, but are useful supplements and adjuncts.

Other Gastrointestinal Conditions. Other gastrointestinal conditions have responded less satisfactorily to anticholinergic treatment, but have shown some response. Some patients with irritable colon have reacted favorably. Some patients with regional enteritis and ulcerative colitis have had less diarrhea and cramps on the drug, while others have noted no improvement. Two patients with chronic pancreatitis have been helped considerably, one patient returning to work for the first time in 12 months. Patients with a "hyperacidity syndrome" (i.e. a typical ulcer story but with no demonstrable ulcer) have responded well. The use of the drugs in severe biliary dyskinesia, biliary colic, and severe dumping syndrome should be considered. The drugs are of little value in patients with a "gastric neurosis" or bowel fixation.

Urology and Anesthesia. There are a few conditions outside of the gastrointestinal tract in which these drugs may be helpful. Engel¹⁷ has found them helpful in patients with irritable bladders and certain types of cystitis. He has found that frequently they will relieve the pain of ureteral colic caused by ureteral calculus, and may relax the ureters sufficiently to allow the stone to pass without causing any further pain. O'Malley and Owens¹⁸ have reported

a beneficial effect of Banthine in patients with enuresis. Wasmuth and Hale⁹ have reported Banthine given intravenously decreased the nausea and vomiting and increased the pulse rate in bradycardia associated with spinal anesthetics. Patients with hyperhydrosis or hypersalivation can expect some relief from these drugs.

As Kirsner and Palmer¹⁰ have pointed out, the ideal gastric anti-secretory drug is not available at the present time. Nonetheless, we have at hand now drugs that are capable of affecting gastric acid secretion and profoundly affecting gastrointestinal motility. The relatively inert compounds previously available cannot be compared with the group of new anticholinergic drugs. These medicines still have a rather wide range of action. If drugs can be devised that are more selective in action (i.e. that affect the stomach, but cause no dryness, or changes in the eye or colonic and bladder motility, or that affect acid secretion of the stomach but not the motility and vice versa) many clinical problems will be solved. The anticholinergic drugs available at the present time, however, are more selective in action, have a much greater effect on the gastrointestinal tract, and have a wider clinical application than any previously available medicine.

SUMMARY

Clinical experience with six new, anticholinergic, antispasmodic drugs in a total of 201 patients has been reviewed. In the doses used, Pamine and Probanthine were the most effective in patients with duodenal ulcer. These drugs are regarded not as substitutes to routine ulcer therapy, but as extremely useful adjuncts. With the use of these drugs the number of patients requiring surgery has decreased. Suggested dosage, indications, and contraindications of the anticholinergic drugs are discussed. It is hoped that in the future similar compounds with even more specificity of action will be available.

References

1. Sippy, B. W.: Gastric and duodenal ulcer: Medical cure by an efficient removal of gastric juice corrosion. *J.A.M.A.* **64**:1625-1630 (May 15) 1915.
2. Levin, E., Kirsner, J. B., Palmer, W. L. and Butler, C.: Comparison of nocturnal gastric secretion in patients with duodenal ulcer and in normal individuals. *Gastroenterology* **10**:952-964 (June) 1948.
3. Levin, E., Kirsner, J. B., Palmer, W. L. and Butler, C.: Nocturnal gastric secretion; studies on normal subjects and on patients with duodenal ulcer, gastric ulcer, and gastric carcinoma. *Arch. Surg.* **56**:345-356 (March) 1948.
4. Woodward, E. R., Harper, P. V., Jr., Tovee, E. B. and Dragstedt, L. R.: Effect of vagotomy on gastric secretion in man and experimental animals. *Arch. Surg.* **59**:1191-1212 (Dec.) 1949.
5. Dragstedt, L. R., Oberhelman, H. A., Jr. and Woodward, E. R.: Physiology of gastric secretion and its relation to ulcer problems. *J.A.M.A.* **147**:1615-1620 (Dec. 22) 1951.
6. Longino, F. H., Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: Orally effective quaternary amine, banthine, capable of reducing gastric motility and secretions. *Gastroenterology* **14**:301-313 (Feb.) 1950.
7. Smith, C. A., Woodward, E. R., Janes, C. W. and Dragstedt, L. R.: Effect of Banthine

ANTICHOLINERGIC DRUGS

- on gastric secretion in man and experimental animals. *Gastroenterology* **15**:718-726 (Aug.) 1950.
8. Brown, C. H. and Collins, E. N.: Use of banthine in treatment of duodenal ulcer; preliminary report. *Cleveland Clin. Quart.* **17**:234-241 (Oct.) 1950.
9. Brown, C. H. and Collins, E. N.: Use of banthine in the treatment of duodenal ulcer; preliminary report on its use in 137 patients. *Gastroenterology* **18**:26-35 (May) 1951.
10. Kirsner, J. B. and Palmer, W. L.: Newer gastric antisecretory compounds. *J.A.M.A.* **151**:798-805 (March 7) 1953.
11. Sleisenger, M. N., Eisenbud, M., and Almy, T. P.: Comparative potency of newer anticholinergic drugs in man, as determined by a sigmoid balloon technique. Read at the National Meeting of the Am. Fed. for Clin. Res. May 4, 1952. To be published.
12. Brown, C. H. and Hoerr, S. O.: Treatment of duodenal ulcer. *Postgrad. Med.* **12**:308 (Oct.) 1952.
13. McHardy, G., Bechtold, J. E. and Browne, D. C.: Evaluation of newer anticholinergics in gastroenterology: secretory, motility and clinical studies on darstine, pamine, and reltine. *J. Louisiana State Med. Soc.* **105**:174 (May) 1953.
14. Rogers, M. P. and Gray, C. L.: A new anti-ulcer drug: A clinical and radiological evaluation. *Am. J. Dig. Dis.* **19**:180-185 (June) 1952.
15. Chamberlin, D. T.: Clinical evaluation of bentyl hydrochloride, new antispasmodic. *Gastroenterology* **17**:224-225 (Feb.) 1951.
16. Collins, E. N.: Personal communication.
17. Engel, W. J.: Personal communication.
18. O'Malley, J. F. and Owens, R. H.: Banthine therapy for enuresis. *Missouri Med.* **50**:161 (March) 1953.
19. Wasmuth, C. E. and Hale, D. E.: Continuous spinal anesthesia in the poor risk and aged surgical patient. *Cleveland Clin. Quart.* **18**:93-97 (April) 1951.

VITAMIN A INTOXICATION

MARY T. HARRISON, M.D.* and ROBERT D. MERCER, M.D.

Department of Pediatrics

THE clinical entity of hypervitaminosis A was first described in 1944 by Josephs.¹ In 1947 Toomey and Morissette² published a study conducted with excellent controls which clearly established the etiology of the disease. Since that time, the diagnosis has been made with increasing frequency, with a total of 24 cases reported to date.³⁻¹⁶

Three clinical factors must be established before the diagnosis can be made: (1) a clear-cut history of excessive intake of vitamin A; (2) elevated levels of vitamin A in the blood; and (3) roentgenographic evidence of subperiosteal new bone formation. Other clinical manifestations which have been reported include hyperirritability, pruritus, rash, alopecia, tenderness over the long bones, cheilosis, and bleeding tendency.

In all cases reported there was rapid improvement in clinical appearance after the vitamin concentrate was eliminated from the diet. The bone changes disappeared also, but this was a much slower process and required a number of months.

The following case is presented as an example of this syndrome.

CASE REPORT

A 28 month old boy was admitted to the hospital on March 17, 1953, because of fever of ten days' duration. He had been in good health until ten days prior to admission when his temperature rose to between 102 and 103 degrees F., the lips cracked and bled, and an ill-defined rash appeared on the face and anterior chest wall. Intense pruritus developed and resulted in deep excoriations of the skin of the arms, legs and trunk. The patient complained of pain in his penis, and a fissure on the glans penis was noted by the mother. Painful lumps appeared on both forearms and on the outer aspect of both feet. He walked "like a baby taking his first steps." The feet swelled so much that the shoes could not be worn. There was extreme irritability, restlessness and whining. At the onset of fever an injection of penicillin was given and antipyretics were started. For several weeks prior to the onset of the illness there had been mild constipation.

The family history was non-contributory. The birth and development had been entirely normal.

There had been an intake since the neonatal period of as much as 1 to 2 teaspoonfuls of Oleum Percomorph (Mead-Johnson) daily. One teaspoonful of this vitamin A-D concentrate provides 200,000 u. vitamin A and 30,000 u. vitamin D.

Physical Examination. The child was acutely ill. The rectal temperature was 101 degrees F., the pulse rate 120 per minute, and the respiratory rate 30 per minute. The blood pressure was 140 systolic (crying). The skin was hot and dry and showed

*Fellow in the Department of Pediatrics.



Fig. 1. Photograph of patient. Note fissuring of lips.

many deep excoriations. The lips were red and fissured with much bloody crusting (fig. 1). On both forearms along the ulnar shafts there were hot, tender, egg-sized swellings (fig. 2). Similar swelling was noted in the region of the fifth metatarsals of both feet.

The head was symmetrical and not enlarged. No pathologic changes were seen in the eyes, ears, nose and throat. There was moderate enlargement of the cervical, axillary and inguinal lymph nodes. The lungs were clear on percussion and auscultation. The heart was normal in size; the heart sounds were of good quality and a soft systolic pulmonic murmur was heard. The abdomen was normal in contour and soft. The liver was palpated 3 cm. below the right costal margin. The spleen was not felt. There was a small fissure at the urethral meatus. The rectal examination was normal. The child refused to stand or walk during the examination. The neurologic examination revealed no abnormalities.

Laboratory Studies. The red blood cell count was 4,380,000 per cu. mm., the hemoglobin content 11 Gm., and the white blood cell count 9200 per cu. mm. with 75 per cent neutrophils, 15 per cent lymphocytes and 10 per cent monocytes. Several urinalyses and stool examinations were normal. The sedimentation rate was 1.1 mm./min. The fasting blood sugar content was 83 mg. per hundred cc., and the blood ascorbic acid level was 0.26 per hundred cc. The Wassermann and serologic tests for lupus erythematosus were negative. Blood and stool cultures showed no pathogenic organisms. The vitamin A blood level was 4 plus elevated on the basis of a semi-quantitative test.¹⁷

X-ray Examination. X-rays of the chest and skull were reported as normal. Films of the upper extremities showed symmetrical cortical hyperostoses of the ulnas (fig. 3). Similar hyperostotic changes were present in the right fifth and left fourth and fifth

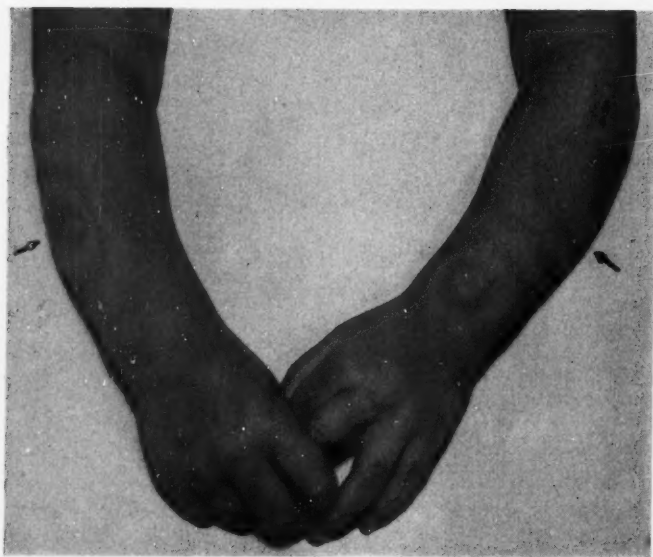


Fig. 2 Photograph of forearms. Note swelling over ulnar regions.



Fig. 3. X-rays of forearms demonstrate hyperostotic changes on ulnar bones.

VITAMIN A INTOXICATION

metatarsals (fig. 4). Because of the increased lines of density at the lower ends of the ulnas, it was believed that healing rickets or scurvy was also present.

Course. Diagnoses of hypervitaminosis A and subclinical scurvy were made. Therapy consisted only of an adequate diet and 50 mg. of ascorbic acid daily. Within several days the child was much improved. There have been several follow-up examinations, the latest one on July 8, 1953, four months after admission, at which time the patient was clinically well. X-ray studies at this time showed much improvement with only minimal periosteal changes in the metatarsals.



Fig. 4. X-rays of feet demonstrate hyperostotic changes on metatarsal bones.

DISCUSSION

The diagnosis of hypervitaminosis A can be made readily if the syndrome is kept in mind and if a careful history of vitamin intake is routinely taken. The essential clinical features are pruritus, cheilosis, hyperirritability, and swellings of forearms and feet. The roentgenographic changes resemble those of infantile cortical hyperostosis, from which it must be differentiated. Thus far, vitamin A intoxication has not been reported to involve the mandible, which is usually reported in infantile cortical hyperostosis. Vitamin A intoxication is rarely seen before the age of 18 months, whereas the diagnosis of infantile cortical hyperostosis can usually be made before the age of six months. Children with this latter disease have been reported to show remission in symptoms while taking large amounts of vitamin A. Caffey⁶ has pointed out that the predilection in hypervitaminosis A for "exposed bones," such as ulnas, fifth metatarsals,

fibulas, and clavicles, would tend to support the theory that the changes may be related in part to trauma.

One cannot emphasize too strongly the need for careful instruction of mothers in the correct dosage of vitamin A concentrates. The mother of our patient was not aware of any danger in overdosage and was of the opinion that "if the boy doesn't eat, he probably needs more vitamins." The result of this rationalization was the daily use of 10 to 20 times the usual amount of A-D concentrate. A six month old sibling who was receiving the same dosage of vitamin A did not show bony changes demonstrable by x-ray or increased blood vitamin A level. Apparently the clinical picture results from overdosage with vitamin A for a long period of time.

SUMMARY

A case of vitamin A intoxication in a 28 month old child is presented. The principal clinical manifestations were hyperirritability, cheilosis, pruritus, and swelling along the ulnas and along the fifth metatarsals. Roentgenographic evidence of subperiosteal new bone formation as well as high blood vitamin A levels helped to confirm the diagnosis. Prompt relief of symptoms followed the withdrawal of vitamin A.

References

1. Josephs, H. W.: Hypervitaminosis A and carotenemia. *Am. J. Dis. Child.* **67**:33-43 (Jan.) 1944.
2. Toomey, J. A. and Morissette, R. A.: Hypervitaminosis A. *Am. J. Dis. Child.* **73**:473-480 (April) 1947.
3. Arena, J. M., Sarazen, P., Jr. and Baylin, G. J.: Hypervitaminosis A; report of unusual case with marked craniotabes. *Pediatrics* **8**:788-794, 1951.
4. Bair, G.: Chronic vitamin A poisoning; report of case. *J.A.M.A.* **146**:1573-1574 (Aug. 25) 1951.
5. Berrey, B. H.: Postinfantile cortical hyperostosis with subdural hematoma; report of case and review of literature. *Pediatrics* **6**:78-85 (July) 1950.
6. a) Caffey, J.: Chronic poisoning due to excess of vitamin A. Description of clinical and roentgen manifestations in 7 infants and young children. *Pediatrics* **5**:672-687 (April) 1950.
b) Caffey, J.: Chronic poisoning due to excess of vitamin A; description of clinical and roentgen manifestations in 7 infants and young children. *Am. J. Roentgenol.* **65**:12-26 (Jan.) 1951.
7. Dickey, L. B. and Bradley, E. J.: Hypervitaminosis A; case report. *Stanford M. Bull.* **6**:345-348 (May) 1948.
8. Fried, C. T. and Grand, M. J. H.: Hypervitaminosis A. *Am. J. Dis. Child.* **79**: 475-486 (March) 1950.
9. Goldzier, S. E., Pisacano, J. C. and Wald, A. M.: Hypervitaminosis A. *J. Ped.* **41**:198, 1950.
10. Gribetz, D., Silverman, S. H. and Sobel, A. E.: Vitamin A poisoning. *Pediatrics* **7**:372-384 (March) 1951.
11. Naz, J. F. and Edwards, W. M.: Hypervitaminosis A; case report. *New England J. Med.* **246**:87-89 (Jan. 17) 1952.

VITAMIN A INTOXICATION

12. Reyersbach, G. C., Hanelin, J. and Joplin, R. J.: Vitamin A intoxication; report of case. *New England J. Med.* **246**:978-980 (June 19) 1952.
13. Rineberg, I. E. and Gross, R. J.: Hypervitaminosis A with infantile cortical hyperostosis, *J.A.M.A.* **146**:1222-1225 (July 28) 1951.
14. Rothman, P. E. and Leon, E. E.: Hypervitaminosis A; report of 2 cases in infants. *Radiology* **51**:368-374 (Sept.) 1948.
15. Sulzberger, M. B. and Lazar, M. P.: Hypervitaminosis A; report of case in adult. *J.A.M.A.* **146**:788-793 (June 30) 1951.
16. Wyatt, T. C., Carrabello, C. A. and Fletcher, M. E.: Hypervitaminosis A; report of case. *J.A.M.A.* **144**:304-305 (Sept. 23) 1951.
17. Josephs, H. W.: Studies in vitamin A; relation of vitamin A and carotene to serum lipids. *Bull. Johns Hopkins Hosp.* **65**:112-124 (July) 1939.

RESPONSES TO CORTICOTROPIN (ACTH) AND CORTISONE IN THROMBOCYTOPENIC STATES

JAMES S. HEWLETT, M.D. and THORNTON SCOTT, M.D.*

Department of Medicine

SPLENECTOMY, considered to be the treatment of choice in idiopathic thrombocytopenic purpura (ITP), has not been attended by uniformly favorable results. Corticotropin (ACTH) and cortisone have recently been found to be effective in some instances of this disorder. This paper summarizes observations on 12 patients with thrombocytopenia of various types, and demonstrates the ability of the steroid hormones to reduce hemorrhagic tendencies even in the absence of a platelet response.

RESULTS

Of the 12 patients, seven had ITP (Table 1), three had thrombocytopenia following drug ingestion, one had thrombocytopenia associated with disseminated lupus erythematosus, and one had chronic lymphocytic leukemia treated by irradiation therapy (Table 2). All received corticotropin or cortisone or a combination of the two.

A sustained clinical and hematologic remission was not obtained in any of the seven patients who had ITP. Two of these received corticotropin alone. One experienced prompt cessation of the bleeding tendency unassociated with a rise in platelets. The other responded with a transient improvement in the hemorrhagic diathesis and a rise in platelets, but relapsed promptly on withdrawal of the drug. This response was obtained in a four year old boy (case 4) who had had a sudden onset of petechiae and epistaxis. The platelet count initially was 61,000 per cu. mm. (Dameshek). On the fourteenth day of treatment the platelet count was 536,000 per cu. mm. Treatment was stopped at this time, and approximately four weeks later the platelet count had dropped to 106,000 per cu. mm.

Four other patients with ITP also received cortisone alone. One responded rapidly with disappearance of purpura and a rise in platelets but relapsed two weeks after therapy was discontinued. Three responded clinically with clearing of the petechiae and cessation of the bleeding, but showed no platelet rise for periods of seven months, 36 days and 21 days, respectively.

The seventh patient with ITP was treated with corticotropin intravenously for one week and experienced remission of all vascular phenomena but failed to exhibit an increase in platelets during a subsequent 55 day course of cortisone.

*Address: 200 West Second Street, Lexington, Kentucky.

Three patients had thrombocytopenia resulting from drug idiosyncrasy. Two of these patients were treated with corticotropin and the third with cortisone. All experienced prompt clinical and hematologic remissions which have persisted 25, 19 and 3 months respectively. An example of the dramatic results occasionally obtained in this type of case was manifested in an 80 year old man (case 10). He had superficial ecchymosis, and hemorrhages into the tissues of the neck and tongue had developed so that he was unable to swallow. The initial platelet count was 24,000 per cu. mm. (Rees-Ecker). Eighteen hours after corticotropin was begun, the tongue was smaller and he was able to swallow, although the platelet count was unchanged. On the sixth day of treatment the platelet count had reached 188,000 per cu. mm. (Rees-Ecker). He has remained well for a subsequent period of one year.

The patient with thrombocytopenia associated with disseminated lupus erythematosus showed a satisfactory response. There was a complete cessation of all bleeding and the platelets returned to a normal level. She was maintained in this remission for a period of 13 months on continued cortisone therapy.

The patient with thrombocytopenia resulting from a combination of chronic lymphocytic leukemia and irradiation therapy obtained relief of active bleeding without significant platelet elevation coincident to corticotropin administration.

DISCUSSION

In this group, steroid therapy was disappointing as a means of inducing complete and permanent remission in ITP. In five of the six patients with "chronic" ITP no hematologic remission was obtained. In the sixth patient, the platelets rose to a normal level during treatment but decreased again when therapy was discontinued. The only patient with "acute" ITP responded on several separate occasions with an adequate platelet elevation which dropped each time to pre-treatment levels shortly after stopping the drug.

In the three instances of thrombocytopenia secondary to drug sensitivity, cortisone or corticotropin therapy was followed by an excellent clinical and hematologic response. Whether this was due entirely to the drug or in large part to withdrawal of the offending drug cannot be stated.

All patients studied experienced relief of the bleeding phenomena and in three this was dramatic. Improvement in capillary resistance as measured by the tourniquet test (Rumpel-Leede), was noted in all patients but could not be correlated with platelet levels or responses. Only two patients in the ITP group showed a prompt and significant platelet rise during treatment. Two patients subsequently had splenectomies. One of these had responded with a complete remission while receiving cortisone but relapsed later. After splenectomy, there was a remission which has lasted seven months. The other patient had had no hematologic improvement while on cortisone, but following splenectomy a satisfactory platelet rise occurred.

Conclusions derived from early reports concerning the use of steroids, although encouraging, have been justifiably cautious. Bethell, Miller and

Meyers¹ were the first to report favorable clinical and hematologic responses in six patients with ITP who were treated with corticotropin. Meyers, Miller, Linman and Bethell² reported further observations on these and 11 additional patients, some of whom were treated with cortisone as well. In 12 of their 17 patients results were described as excellent. Five of their patients continued in remission for periods of 16 to 22 months. Robson and Duthie³ reported clinical improvement without sustained platelet response in two patients with ITP. Faloon, Greene and Lozner⁴ noted complete remission with corticotropin in one of five patients, and varying responses to corticotropin or cortisone in the remaining four patients. They noted improvement in vascular resistance in all cases preceding the rise in platelets, and in some instances, independent of it. Jacobson and Sobier⁵ reported prompt but transient platelet responses to normal levels in three patients with ITP. Wintrobe and others⁶ obtained temporary remission with corticotropin in one patient. Hyman⁷ obtained persistent remission in one patient with corticotropin and transient response in another. Wilson and Eiseman⁸ observed 12 patients and noted sustained improvement in three and transient responses in two. Stefanini et al.⁹ treated 11 patients suffering from ITP and obtained no permanent remissions. They concluded that these hormones reduced the spontaneous bleeding manifestations, improved capillary resistance, shortened the bleeding time, and prolonged the phase of initial vasoconstriction following incision of the skin.

The mechanisms responsible for thrombocytopenia in ITP are obscure. Several different theories have been suggested. Thrombocytopenia has been attributed to: (1) sequestration or phagocytosis of platelets by the spleen; (2) the action of a hypothetical humoral substance produced in the spleen, or elsewhere, capable of suppressing megakaryocytic activity; and (3) a thrombocytopenic factor in plasma which damages circulating platelets and possibly also suppresses the megakaryocytes. Current studies have served to emphasize the latter concept that immunologic factors play a major part in many cases of ITP.¹⁰⁻¹² An immunologic mechanism has also been suggested as an etiologic factor in purpura secondary to certain drugs. For instance, platelet agglutination and lysis, *in vitro*, by the addition of Sedormid to blood of patients who have recovered from Sedormid purpura, have been described.¹³ This was found to result from a plasma factor acting in the presence of Sedormid. A similar mechanism has been observed in purpura due to quinidine. It is generally conceded that the thrombocytopenia in leukemia is predominantly due to a mechanical displacement of the megakaryocytes.

There is little direct evidence that corticotropin and cortisone can directly affect any of these pathogenetic mechanisms. Furthermore, it is difficult to evaluate the actual role of these drugs in ITP since spontaneous remissions can occur. It is necessary to consider the effects of these steroids with regard to two aspects of thrombocytopenia, namely, their effect on capillary resistance, and their effect on platelet production. It has been repeatedly observed that improvement in hemostasis and vascular resistance in ITP treated with corticotropin and cortisone may occur despite the persistence of thrombocytopenia.

THROMBOCYTOPENIC STATES

Effect of Steroid Therapy in Seven Patients with Idiopathic Thrombocytopenic Purpura

Case No. and Sex	Age in years	Diagnosis	Therapy mg./day No. days	Platelet count before therapy	Platelet count after therapy (day)	Bleeding phenomena		Remarks
						Before	After	
1 M	11	Idiopathic thrombopenic purpura	Cortisone 200 mg/7 da. 100 mg/14 da. 75 mg/14 da.	10,000	18,000 (7)	++	+	No response; remission followed splenectomy. (1 mo.)
2 F	8	Idiopathic thrombopenic purpura	Cortisone 100 mg/9 da. 50 mg/5 da.	46,000	140,000 (14)	++	0	Clinical and hematologic response with prompt relapse. Remission following splenectomy. (7 mo.)
3 F	21	Idiopathic thrombopenic purpura.	ACTH 80 mg/10 da.	100,000	100,000 (10)	++++	0	Prompt clinical remission. Gradual platelet rise over 1 yr. period.
4 M	4	Idiopathic thrombopenic purpura	ACTH 60 mg/4 da. 40 mg/7 da.	61,000	536,000 (14)	++	0	Complete remission. Relapse in 1 mo.
5 F	17	Idiopathic thrombopenic purpura	Cortisone 200 mg/7 da. 100 mg/14 da.	80,000	33,000 (21)	++	0	Petechiae disappeared. No hematologic improvement.
6 M	30	Idiopathic thrombopenic purpura	ACTH I.V. 20 mg/6 da. cortisone 200 mg/10 da. 100 mg/14 da. 75 mg/21 da.	11,000	33,000 (31)	++	+	Petechiae improved. No hematologic changes.
7 F	15	Idiopathic thrombopenic purpura	Cortisone 200 mg/21 da. 100 mg/7 da.	17,000	40,000 (14)	++	0	Petechiae disappeared. No significant platelet rise.

Table 2
Effect of Steroid Therapy in Five Patients with Secondary Thrombocytopenic Purpura

Case No. and Sex	Age in years	Diagnosis	Therapy mg./day No. days	Platelet count before therapy	Platelet count after therapy (day)	Bleeding phenomena		Remarks
						Before	After	
8 F	15	Disseminated lupus erythe- matosus	ACTH 40 mg/10 da.	20,000	192,000 (8)	++++	0	Remission maintained 1 yr. Pa- tient later placed on maintenance cortisone.
9 M	45	Drug idio- syncrasy	ACTH 80 mg/4 da. 40 mg/2 da.	< 10,000	100,000 (9)	++++	0	Remission maintained 25 mo.
10 M	80	Drug idio- syncrasy	ACTH 100 mg/5 da. 40 mg/3 da.	24,000	188,000 (6)	++++	0	Complete remission - sustained for 1 yr. +.
11 F	48	Drug idio- syncrasy	Cortisone 300 mg/7 da. 200 mg/4 da. 100 mg/10da.	< 10,000	100,000 (10)	++++	+	Complete remission - 3 mo. follow-up.
12 M	63	Chronic lymphocytic leukemia - irradiation thrombopenia	ACTH I.V. 20 mg/10 da.	20,000	20,000 (10)	++++	0	Clinical remission. No platelet rise. 3 mo. follow-up.

This suggests a dual effect of these drugs on thrombocytopenic purpura. Robson and Duthie³ have demonstrated increased capillary resistance following various kinds of stress and trauma which they attributed to adrenal cortical activity. Improvement in vascular resistance may also occur following splenectomy in the absence of a platelet response. It has been repeatedly observed in patients with ITP receiving adrenal steroids, that capillary resistance increases prior to, or in the absence of, a rise in platelets. Corticotropin and cortisone have been shown to lessen vascular permeability in various conditions, although capillary permeability itself has not been incriminated in ITP.¹⁴ The adrenal steroids in some way alter the capacity of tissues to react characteristically to the irritative action of antigen-antibody combinations. These drugs have been found to induce remission in allergic purpura not associated with thrombocytopenia. Should a state of hyperimmunity involving the capillary walls underlie some of the phenomena in thrombocytopenic purpura, a passive mode of action of these hormones could be postulated without regard to the platelet level.

The second aspect of thrombocytopenia as related to corticotropin and cortisone involves their action on platelet production. Their effect has been irregular although reports in the literature indicate that some patients with thrombocytopenic states respond to the drugs with an increase in platelet production. It is possible that these hormones control an "immuno-thrombocytopenia" by suppression of a platelet antibody, similar to their effect in certain cases of acquired hemolytic anemia associated with a positive antiglobulin test. Harrington and his group¹² observed a complete remission in ITP from cortisone which was associated with disappearance of the thrombocytopenic factor. Emphasizing another possible mode of action, Bethell¹ has stated that the spleen exerts a "regulatory action susceptible to derangement" on the maturation and release of thrombocytes and that this function may be under the control of the adrenal cortex. Another mechanism postulated to explain the action of corticotropin and cortisone involves their capacity to stimulate myeloid elements. Harrington¹² mentioned two patients without demonstrable platelet agglutinins who responded to these agents. He presumed in these cases that the hormones stimulated an increased rate of platelet formation from megakaryocytes. It is possible, as Meyers² suggests, that the adrenal hormones in thrombocytopenia restore "hematopoietic equilibrium" through a combination of effects including non-specific action on capillary fragility, modification of responses to antigen-antibody combinations and stimulation of the megakaryocytes.

SUMMARY AND CONCLUSIONS

Observations were made on 12 patients with thrombocytopenia of various etiology who were treated with corticotropin or cortisone.

Improvement in capillary fragility and bleeding phenomena occurred in all seven patients with ITP. Five showed no rise in platelets. Two exhibited a transient rise in the platelet count, but relapsed when therapy was discontinued.

Satisfactory clinical and hematologic remission was demonstrated in each

of three patients with purpura secondary to drug sensitivity, and in a patient with acute lupus erythematosus.

Complete cessation of the hemorrhagic tendency, without a concomitant platelet rise, occurred in one patient with chronic lymphocytic leukemia.

Corticotropin and cortisone exert a beneficial effect on capillary fragility and bleeding phenomena in various types of thrombocytopenia. The improvement is not necessarily associated with an increase in circulating thrombocytes.

Observations indicate that these agents are useful in controlling severe bleeding in ITP, in secondary thrombocytopenia and in the preparation of patients for splenectomy. As a means of inducing a permanent remission in ITP, however, steroid therapy has been disappointing.

References

1. Bethell, F. H.,¹ Miller, S., Meyers, M. C.: Administration of ACTH and Cortisone in Hypersplenic Syndromes. Proceedings of the Second Clinical ACTH Conference, vol. 2, New York, The Blakiston Company, 1951, pp. 173-180.
2. Meyers, M. C., Miller, S., Linman, J. W. and Bethell, F. H.: Use of ACTH and cortisone in idiopathic thrombocytopenic anemia. *Ann. Int. Med.* 37:352-361 (July) 1952.
3. Robson, H. N., and Duthie, J. J. R.: Capillary resistance and adreno-cortical activity. *Brit. M. J.* 2:971-977 (Oct. 28) 1950.
4. Faloona, W. W., Greene, R. W. and Lozner, E. L.: Hemostatic defect in thrombocytopenia over cortisone. *Am. J. Med.* 13:12-20 (July) 1952.
5. Jacobson, B. M. and Sobier, W. D.: Effects of ACTH and of cortisone on platelets in idiopathic thrombocytopenic purpura. *New England J. Med.* 246:247-249 (Feb. 14) 1952.
6. Wintrobe, M. M., Cartwright, G. E., Palmer, J. G., Kuhns, W. J. and Samuels, L. T.: Effects of ACTH and cortisone on blood in various disorders in man. *Arch. Int. Med.* 88:310-336 (Sept.) 1951.
7. Hyman, G. A.: In "Hypersplenism," Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, *Am. J. Med.* 11:494-506 (Oct.) 1951.
8. Wilson, W. J. and Eiseman, G.: Effects of corticotropin (ACTH) and cortisone on idiopathic thrombocytopenic purpura. *Am. J. Med.* 13:21-26 (July) 1952.
9. Stefanini, M., Sontag, E. P., Choeterjea, J. B., Dameshek, W. and Solomon, L.: Corticotropin (ACTH) and cortisone in idiopathic thrombocytopenic purpura. *J.A.M.A.* 149:647-653 (June 14) 1952.
10. Evans, R. S., Takahashi, K., Duane, R. T., Payne, R., and Liu, C.: Primary thrombocytopenic purpura and acquired hemolytic anemia: Evidence for common etiology. *Arch. Int. Med.* 87:48-65 (Jan.) 1951.
11. Harrington, W. J., Minnich, V., Hollingsworth, J. W., and Moore, C. V.: Demonstration of thrombocytopenic factor in blood of patients with thrombocytopenic purpura. *J. Lab. & Clin. Med.* 38:1-10 (July) 1951.
12. Harrington, W. J., Sprague, C. C., Minnich, V., Moore, C. V., Ahlvin, R. C. and Dubach, R.: Immunologic mechanisms in idiopathic and neonatal thrombocytopenic purpura. *Ann. Int. Med.* 38:433-469 (March) 1953.
13. Ackroyd, J. F.: Pathogenesis of thrombocytopenic purpura due to hypersensitivity to Sedormid (allyl-isopropyl-acetyl-carbomide). *Clin. Sc.* 7:249 (April 19) 1949.
14. Wedgewood, R. J., Hawn, C., and Janeway, C. A.: Mechanism of action of ACTH in experimental nephritis due to foreign protein. Proceedings of the Second Clinical ACTH Conference, vol. 1, New York, The Blakiston Company, 1951, pp. 108-114.
15. Stefanini, M., Roy, C. A., Zannos, L. and Dameshek, W.: Therapeutic effect of pituitary adrenocortical hormone (ACTH) in a case of Henoch-Schönlein vascular (anaphylactoid) purpura. *J.A.M.A.* 144:1372-1374 (Dec. 16) 1950.

LENS IN ANTERIOR CHAMBER OF THE EYE: SURGICAL REMOVAL

ROBERT L. ALEXANDER, M.D. and ROSCOE J. KENNEDY, M.D.

Department of Ophthalmology

IMMEDIATE surgical intervention is mandatory in patients with the lens located in the anterior chamber of the eye because of the frequent complications of glaucoma and secondary iritis. Yet, because of the rare occurrence of this condition, many surgeons are not prepared to perform the required operation.

During a five year period at the Cleveland Clinic, five cases were seen with lens dislocated in the anterior chamber, four were operated. The fifth was not operated because the eye was blind and the lens partially absorbed. Those patients with a lens dislocated behind the iris diaphragm are not included since this type of posterior lens dislocation requires a different surgical approach.

McDonald¹ in a report of 94 cases of all types of dislocated lens seen at Wills' Eye Hospital during a five year period found only three instances of dislocation in the anterior chamber, the remainder presumably being dislocated into the vitreous.

The following case reports are representative of those patients seen at the Clinic with this condition.

CASE REPORTS

Case 1. This 42 year old woman is illustrative of those patients with traumatic dislocation of the lens into the anterior chamber. Two months prior to examination she had bumped her head on a kitchen cabinet door. The right eye had been slightly painful following the accident but the pain slowly subsided. Two weeks before examination, the eye suddenly became painful and red. She obtained no relief from home remedies.

Positive physical findings were confined to the right eye, the upper lid of which was slightly edematous. The intra-ocular tension of the eye was 70 mm. Hg. Schiotz. The conjunctiva showed superficial and ciliary injection. The cornea showed bedewing throughout. The anterior chamber was filled with the partially opaque lens that touched the cornea. The base edge of the iris was visible. No fundus view could be obtained.

Case 2. This 64 year old woman is illustrative of those who experience no pain although the lens is in the anterior chamber. At examination the patient complained of blurring vision in the right eye and occasional double vision. The symptoms had been present for two years. There was no history of trauma. The eyes had been neither painful nor red. The positive physical findings were confined to the right eye. Vision in the right eye was hand movement at 1½ M., the tension ranged from 24 to 27 mm. Hg. Schiotz. The conjunctiva and cornea were clear. In the anterior chamber lay a partially calcified lens (fig. 1a). Part of the fundus could be viewed behind the lens and it showed an inactive chorioiditis.

This case is of particular interest because it is possible that this patient had a lens in the anterior chamber for two years and yet did not develop glaucoma. In addition, the cornea remained unchanged with the lens resting against its posterior surface.

Three other cases were seen: one in a four year old boy with the lens previously dislocated behind the iris who had a spontaneous luxation of the lens into the anterior chamber of the left eye; one in an 18 year old man who had Marfan's syndrome, followed for ten years, who had a spontaneous luxation into the anterior chamber of the left eye; one in a 75 year old woman who did not have a previously known dislocated lens but developed a spontaneous dislocation of the lens into the left anterior chamber.

PRINCIPAL SURGICAL PROCEDURES

In the surgical removal of a lens four considerations are immediate and important: (1) prevention of loss of lens into posterior chamber; (2) prevention of a loss of vitreous; (3) prevention of entrance of vitreous into anterior chamber; and (4) prevention of future complications in the eye.

A successful technic consists essentially of the following:

1. Use of a strong miotic, such as di-isopropyl fluorophosphate, that produces a pin-point pupil and brings the iris down behind the lens.
2. Use of a preplaced suture at the corneoscleral junction.
3. Careful opening of the chamber as follows:
 - a. Make a small incision at 12 o'clock with a von Graefe knife in such a manner that the blade does not come near the lens. A keratome must never be used because of the danger of its penetrating the lens as it enters the chamber.
 - b. Enlarge the wound with scissors. This opening must be large enough to allow the lens to be delivered without distortion.
4. Use of a Verhoeff type or Arruga type of cataract forceps to grasp the nearest edge of the capsule lightly and gently pull it forward. No counter pressure at 6 on the limbus will be needed, as the lens is free in the chamber and needs only slight traction to guide it out through the wound.
5. By drawing the suture taut behind the lens as it is delivered, the lens is prevented from slipping back into the anterior chamber.
6. Careful inspection of the anterior chamber for evidence of vitreous herniation through the pupil after the lens is delivered.
7. Performance of a large peripheral iridectomy leaving the sphincter border intact. An iridectomy of this type is chosen to prevent the development of glaucoma or iris prolapse.
8. The rest of the procedure and hospital course is the routine followed for any intracapsular cataract surgery.

The completed operation appears as illustrated in figure 1b.

Kirby² in his brief discussion of the luxation of the lens into the anterior chamber stated that the lens "may be withdrawn by traction with suitable

LENS IN ANTERIOR CHAMBER OF EYE

(a)



(b)



Fig. 1. (Case 2) (a) Partially calcified lens in anterior chamber. (b) One year after surgery.

forceps, suction cup, or with a loop." The forceps is all that is usually indicated, for if a suction cup is introduced it takes so much room in the anterior chamber that the lens is forced backward against the iris endangering the location of the dislocated lens. In this way the lens might be forced back through the pupil and into the vitreous cavity. The suction cup might be applied to the posterior surface of the lens to force the lens against the cornea, and the suction cup acts as a loop. The loop could be used as suggested by Kirby but here enters the danger that it will engage the free iris border and pass into the posterior chamber. In this series, forceps has been found adequate for it has provided guidance to the lens in removing it from the chamber and the slight traction necessary for extraction. Since the lens is lying free in the anterior chamber, it needs little help to deliver itself. The forceps permits a lens extraction with minimal possible trauma to the tissue, one of the first considerations of the ophthalmic surgeon.

Duke-Elder³ said that in these cases "miotics are to be avoided, indeed,

eserine may precipitate a glaucomatous attack." This is contrary to our experience for we have successfully employed strong miotics to produce a small pupil. This caused the iris to act as a diaphragm holding the lens in the anterior chamber until entrance could be effected and the misplaced lens delivered. For this reason case 1 was chosen to illustrate that in the presence of glaucoma, a miotic could be used until the lens was delivered. The patient's postoperative course was not affected. In no patient did the miotic cause glaucoma but in patients where glaucoma existed it did not relieve the disease. Conversely, atropine may dilate the pupil to such an extent that the lens is permitted to luxate into the posterior chamber or vitreous.

The patients must be carefully followed for evidence of continued or secondary glaucoma. Case 1 was given $\frac{1}{4}$ per cent eserine daily for the two weeks immediately following her discharge from the hospital. It was then discontinued and has not been resumed for the past five years. Case 2 had no elevation of intra-ocular tension for three years after operation.

SUMMARY

The important steps in the care of patients with the lens dislocated in the anterior chamber of the eye are:

1. Operate and remove the lens as soon as miotics have reduced the pupil size.
2. Remove the lens in capsule.
3. Perform a large peripheral iridectomy.
4. Insist upon a close follow-up for years after the operation.

References

1. McDonald, P. Robb and Purnell, J. E.: The dislocated lens. Transactions of the Section of Ophthalmology of the A.M.A. at the Ninety-Ninth Annual Session, San Francisco, June 26-30, 1950, 'A.M.A., Chicago, Illinois, pp. 56-74.
2. Kirby, D. B.: Development of system of intracapsular cataract extraction. *Am. J. Ophth.* 27:124-136 (Feb.) 1944.
3. Duke-Elder, Stewart: Text-Book of Ophthalmology, vol. 3, St. Louis, C. V. Mosby Co. 1947, pp. 3308-3309.

END RESULTS IN RETINAL DETACHMENT SURGERY

ROSCOE J. KENNEDY, M.D. and PHILIP KAZDAN, M.D.*

Department of Ophthalmology

SINCE Gonin's publication¹ in 1929, the treatment of retinal detachments has received much attention in the literature and varying results have been reported.

In a symposium presented at the Fifty-Sixth Academy of Ophthalmology and Otolaryngology in October of 1951,² the committee classified complete reattachment of the retina for a period of not less than six months as a cure (anatomic viewpoint). As they pointed out, this is purely an arbitrary time limit, but it seems to be a fair one. Retinal reattachment does not necessarily mean visual improvement, as we will show.

A statistical survey of end results following operation in 103 consecutive cases of retinal detachment seen at the Cleveland Clinic is presented. The report of results is based on the forementioned criterion.

PREOPERATIVE FACTORS

Age. Ages of the patients showed no significant relationship to incidence although the greatest percentage of cases occurred in the fifth, sixth and seventh decades. These patients were slightly older than most of those reported in the literature and this factor may have some influence on success or failure due to vascular degeneration in older age groups.

Incidence According to Age in Years

(103 patients)

(Age range: 9-76)

Age	Incidence
9-20	6
21-30	6
31-40	11
41-50	19
51-60	33
61-70	25
over 71	3

} 77 (or 74.7%)

Sex. Sixty of the patients were men (58.2 per cent) and 43 were women (41.8 per cent); the percentage difference of 16.4 seems insignificant.

Duration of Detachment. From past histories it was found that three days was the shortest duration of detachment, one year the longest (one case); the

*Fellow in the Department of Ophthalmology.

average was two weeks. The greatest percentage of patients (76.7 per cent) reported a duration of less than one month.

Trauma. This factor is probably much less important than is generally believed. There was no direct relationship of trauma to success or failure in these cases. Fifteen (14.5 per cent) of the patients had undergone previous eye surgery; ten (9.7 per cent) had experienced direct trauma, and eight (7.8 per cent) indirect trauma. Seventy (67.9 per cent) had no history of trauma.

Occupation. This factor appeared unrelated to incidence. Sixty-four of the patients were white-collar workers, 27 laborers, 8 farmers and 4 professional people.

Systemic Diseases. Atopic dermatitis was the only systemic disease which seemed to affect the results of the operation in this series. Only one of six operations performed upon patients who had atopic dermatitis was successful. It must be remembered that in detachment surgery we are not treating the systemic or degenerative disease.

Systemic Disease	Incidence	No. of Successful Reattachments
Hypertension	9	3
Atopic dermatitis	6	1
Hyperthyroid	1	0
Diabetes mellitus	3	1
Arthritis	1	0
Poliomyelitis	1	1
Multiple sclerosis	1	0
TOTAL	22	6

Refractive Errors. It is generally believed that myopia, especially of higher degree, has a definite relationship to the degree of success or failure of the operation. In this series in which there were 17 myopes and 19 hyperopes, this was not confirmed.

Bilateral Detachments. Generally, patients who had this condition showed a poor prognosis. They were usually seen after the second eye had become detached. Shipman³ believes that if a patient has a detachment in one eye without explainable cause, he is extremely likely to develop detachment in the other eye in three to ten years.

Eleven patients with bilateral detachment were seen; three were operated upon at the Clinic, two successfully.

Type of Detachment. Seventy-nine cases had billowy detachment; 28 of these with hole. Twenty-four cases had flat detachment; six of these with hole. Hole was found in the superior temporal quadrant in all cases except two in which it was superior nasal in location.

Visual Fields. Preoperative fields agreed with clinical findings. Post-operative fields showed no direct correlation with visual acuity obtained, at least in the early postoperative period.

Mode of Surgery

All patients were operated upon by a combination of surface coagulation and penetrating diathermy. No scleral resections were done.

Postoperative Results

Successful Reattachments. Forty-nine of the 103 patients operated upon were classified as having successful reattachments according to the criterion established by the Ophthalmology and Otolaryngology Committee.² Thirteen of the 103 were lost to follow-up and the figures presented are based on consideration of these 13 as failures. If these 13 cases were disregarded the overall figure would be increased by approximately 10 per cent.

Type of Detachment	No. of Cases Successful	Percentage
Billowy	38	77.7
with hole (10 or 20.5%)		
without hole (28 or 57.2%)		
Flat	11	22.3
with hole (4 or 8.1%)		
without hole (7 or 14.2%)		

Of those cases with hole, 28.6 per cent were successful; of those cases without hole, 71.4 per cent were successful. This greater success of operations in cases of detachment without hole is in contrast to the majority of reports in the literature and is attributed to improved preoperative care which includes adequate preoperative bed rest of approximately five days to allow the retina to fall back into place and permit a more careful search for tears. Of all cases, 47.5 per cent were successful.

Visual Acuity. Visual acuity is the most important criterion of success or failure as far as the patient is concerned. Successful reattachment with decreased vision probably indicates that there has been a detachment or injury of the macula. Of the 49 patients classified as having successful reattachments 5 (10.2 per cent) had no visual improvement, 32 (65.3 per cent) had improvement, and 12 (24.5 per cent) had decreased visual acuity.

Discussion

The cases reviewed represent a group of unselected patients, who in many instances were referred for surgery even though the preoperative prognosis was not good, as in those cases of long duration or with an inadequate history of duration.

Amsler⁴ stated that 60 to 65 per cent of the operations performed upon recent and old cases could be expected to be successful. Duke-Elder⁵ estimated that 50 per cent of cases of detachment could be cured, and in favorable cases, 75 per cent. Shipman³ reported in 1950 that of 431 operations, 46.9 per cent were complete recoveries and 20.6 per cent were improved. The percentage of success is variable depending on the author, his technic and standard for successful reattachment.

Summary

One hundred and three unselected cases of patients with retinal detachment who were operated upon are reviewed and successful results reported for 47 per cent. In this series 13 patients lost to follow-up were regarded as failures. If these 13 were disregarded the percentage would be 57. A careful selection of cases would increase the percentage of successful reattachments.

In contrast to the majority of reports in the literature, operations for retinal detachment without hole were more successful than those for retinal detachment with hole. This greater success is attributed to improved preoperative care, which includes adequate bed rest.

References

1. Gonin, J.: *Le traitement local du décollement rétinien*. In *concilium Ophthalmologicus*. The Hague, Netherlands, Gravenhage, 1929.
2. Post, L. T.: Symposium: retinal detachment. *Tr. Am. Acad. Ophth.* 56:370 (May-June) 1952.
3. Shipman, J. S.: Some practical facts regarding retinal detachment surgery, with report of results in over 400 unselected and consecutive cases. *Am. J. Ophthalmol.* 33:847-860 (June) 1950.
4. Amsler, Marc: *Operations on the Retina*, chap. in Berens, Conrad, editor: *Eye and Its Diseases*. ed. 2, Philadelphia, W. B. Saunders Co., 1949, p. 950.
5. Duke-Elder, W. S.: *Textbook of Ophthalmology*. vol. 3, St. Louis, Mosby, 1941, p. 2920.

MUCOEPIDERMOID CARCINOMA OF SALIVARY GLAND ORIGIN

GEORGE F. STEVENSON, M.D.* and JOHN B. HAZARD, M.D.

Department of Pathology

MUCOEPIDERMOID CARCINOMA, a distinctive neoplasm of salivary gland origin, had received comparatively little consideration in the medical literature until recent years. It is the purpose of this report to review the features of this neoplasm as previously described and to present 12 additional cases.

The first authentic instance of mucoepidermoid carcinoma was reported by Schilling¹ in 1921; the tumor arose in the parotid gland. However, there is some possibility that cases mentioned earlier by Volkmann² and Lecene³ are examples of this tumor. In 1940, in addition to presenting eight cases of mucoepidermoid carcinoma, Skorpil⁴ reviewed the literature and found seven previously reported instances of the neoplasm. In this country, it was not until 1945 that Stewart, Foote and Becker⁵ first described this tumor and recognized it as an entity. In their report they analyzed the data derived from a study of 45 cases of this salivary gland neoplasm, for which they suggested the name mucoepidermoid tumor. In 1948 Lindell⁶ described 12 additional examples and presented a detailed analysis of the reported cases. In 1949 Godwin and Colvin⁷ described two more instances, in 1950 Rawson, Howard, Royster and Horn⁸ mentioned 12, and in 1951 Kirklin, McDonald, Harrington and New⁹ included 19 in a report of parotid tumors in general. Pung¹⁰ added one case in 1952, and in 1953 eight were described in a report by Bauer and Bauer¹¹ and eight more were mentioned by Slaughter, Southwick and Walter.¹² It will be noted that the majority of the case reports have been published during the past decade. In the present review 157 cases were found mentioned in various reports.

INCIDENCE

Despite the rather recent recognition of this tumor, it is of sufficient incidence compared with the better known salivary gland neoplasms to be of considerable importance. The 45 cases reported by Stewart et al.⁵ were encountered among approximately 700 salivary gland tumors, an incidence of slightly more than 5 per cent. In the series of 160 cases of salivary gland neoplasms described by Rawson et al.,⁸ the incidence was 7.5 per cent. Nineteen of the 717 tumors reported by Kirklin et al.⁹ were mucoepidermoid carcinoma, representing 2.6 per cent. Bauer and Bauer¹¹ reported eight cases among 143 salivary gland

*Former Fellow in Department of Pathology, now at Northwestern University Medical School and St. Joseph's Hospital, Chicago, Illinois.

RELATIONSHIP BETWEEN AGE OF PATIENT
AND SITE OF MUCOEPIDERMOID CAR-
CINOMA
(50 CASES)

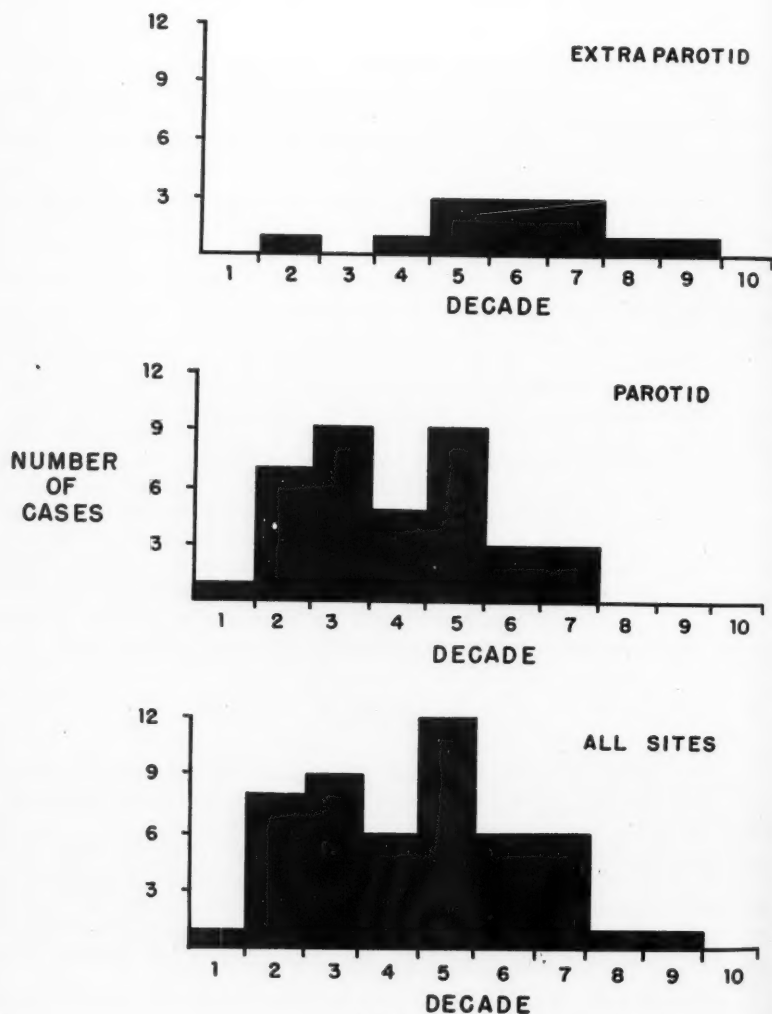


Fig. 1

MUCOEPIDERMOID CARCINOMA

tumors, 5.6 per cent. The ten cases of parotid origin in this report formed 5 per cent of tumors of this gland.

Age. Mucoepidermoid carcinoma of the salivary glands has been described in all age groups. It attains its highest incidence in the fifth decade when all sites are considered (fig. 1).

Sex. In 52 individual reports there were 35 women and 17 men, a ratio of approximately 2 to 1. Stewart et al. found an approximately equal sex distribution.

SITE

Mucoepidermoid carcinoma has been reported in all major salivary glands but in the majority of cases it has arisen in the parotid gland. The sites of origin of 157 cases including those of this report are summarized in Table 1. Of the minor salivary glands those of the tongue were involved most frequently, but neoplasms were found also in the lips, cheeks and palate. Owens¹³ reviewed the cases of tumors of the minor salivary glands published in the 20 years prior to 1949 and found 14 mucoepidermoid tumors among the total of 1138 neoplasms. No record of the occurrence of this neoplasm in the lacrimal gland or other extra-salivary locations has been found.

Table 1

Sites of Origin of Mucoepidermoid Carcinoma		No. of Cases
Site		
Major salivary glands		112
Parotid	105	
Submaxillary	6	
Sublingual	1	
Minor salivary glands		45
Total		157

PATHOLOGY

The neoplasm usually has a maximum diameter of 2 or 3 cm. but may range from a few mm. to 5 cm. The surface may appear rough and irregular or lobulated. Frequently, it lacks circumscription and fuses with adjacent structures. Encapsulation is recorded in a little more than 10 per cent of reported cases. The consistence varies from firm to hard depending on the amount of cyst formation. If cyst formation is marked, it may give the neoplasm a fluctuant character. At operation the first indication of the nature of the tumor may be the appearance of thick mucoid material when the tissue is incised. The tumor tissue is white or pale gray to tan, tough, and occasionally of cartilaginous consistence. It may be solid throughout, but in most instances is partly cystic.

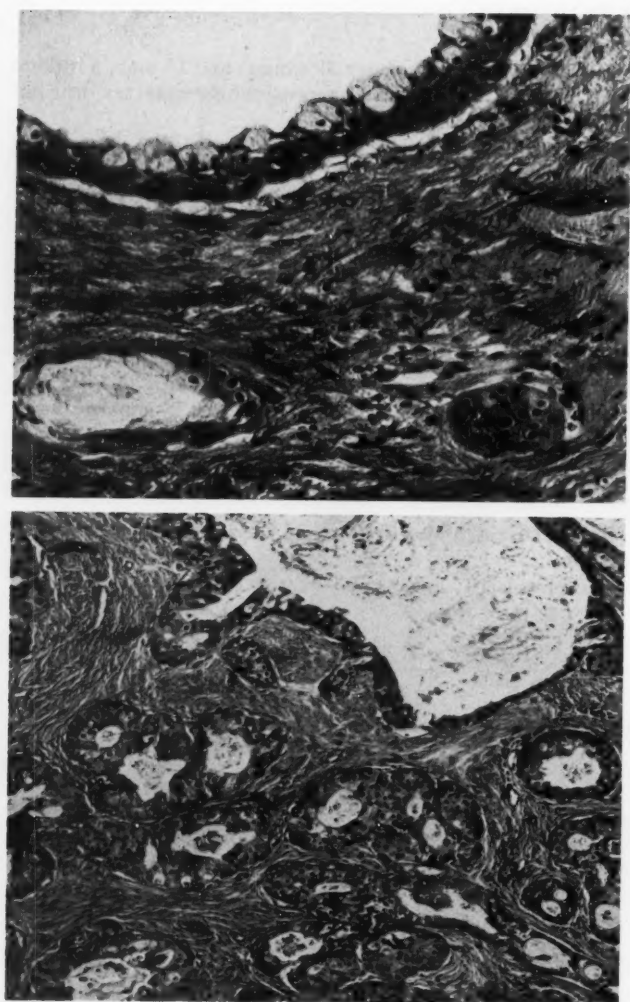


Fig. 2. (Case 8) Mucocystic carcinoma. (a) Small and large mucus-containing lumina lined by intermediate and basal cells and a few mucous cells. X 70. (b) Cyst lined by basal cells surrounded by goblet cells. X 200.



Fig. 3. (Case 7) Sheets of squamous cells with mucus-containing structures formed by goblet cells. X 70.

The microscopic appearance is distinctive. Typically, squamous and mucous cells are arranged in both cystic and solid formations and these cell types are intermingled with small cuboidal to polyhedral cells similar to those in the basal and intermediate positions in the parotid ducts (figs. 2 and 3). Also there may be polyhedral cells with abundant, pale, reticulated cytoplasm, suggestive of sebaceous gland cells. The mucous cells are often of goblet type (fig. 4) and usually line spaces of irregular size and contour. At times the spaces are partly or wholly devoid of lining epithelium and mucus lies in pools in the connective tissue stroma (fig. 5). In the more malignant forms of the tumor, the number of squamous and polyhedral cells is usually increased, arrangement is solid or cord-like, and the stroma is sparse. Commonly the neoplastic cells are well differentiated and show slight nuclear variability; mitoses are rare and tumor giant cells absent. In some tumors the epithelial cells have a pale-staining cytoplasm producing a hypernephroid appearance (fig. 6).

Generally, the epithelial elements are not limited by a capsule and invade the salivary gland tissue and neighboring structures, the latter to a limited extent. Distant metastases are uncommon, but regional and cervical node involvement is frequent.

CLINICAL COURSE

The usual clinical course is one of slow progressive growth, local spread

and regional recurrence. The initial signs and symptoms are similar to those of the common mixed tumor of salivary glands. The first manifestation of the neoplasm is most often a painless swelling of firm rubbery or fluctuant consistence. The mass may be fixed initially or remain well defined and movable for an indefinite period. Other than the presence of a mass there are few subjective findings, although local pain, bloody saliva and facial weakness have been encountered occasionally. Typically, the neoplasm grows slowly and in some instances may remain the same size for prolonged periods. In 43 reported cases, 50 per cent of the patients had noted the presence of a mass for one year or less, about 25 per cent had noted it for more than three years, and slightly less than 10 per cent for 10 to 15 years. In the few instances that growth was rapid from the beginning there was more extensive involvement of the surrounding structures. Regardless of growth rate, invasion of adjacent structures is a common finding, and in neoplasms of the parotid gland involvement of the overlying skin may occur with ulceration and the formation of a salivary-cutaneous fistula. However, this was not a common feature in the cases of this series, occurring in only one instance where there had been operative interference with the tumor in the parotid. When the neoplasm arises in this gland, extensive involvement of the external ear may occur. The more malignant tumors also may invade the deep tissues and involve the bones of the jaw and mastoid region. In such cases cachexia is frequent.

With rare exceptions, recurrences following excision are at the site of the original neoplasm. Of 31 patients traced one year or longer, only seven were without recurrence. The majority of the 24 recurrences were within one year

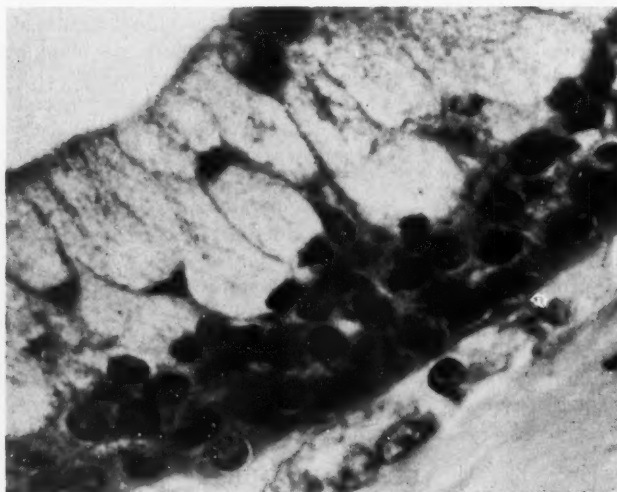


Fig. 4. (Case 2) A portion of wall of cystic structure with lining of goblet cells and basal cells. X 750.

MUCOEPIDERMOID CARCINOMA

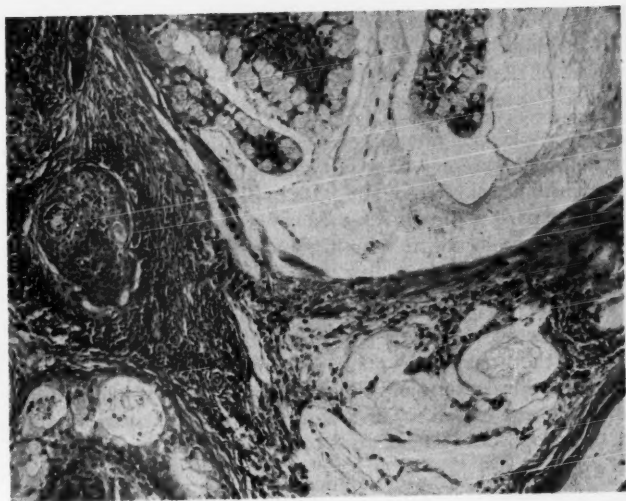


Fig. 5. (Case 7) Pools of mucus in connective tissue stroma adjoining neoplastic islands of goblet and intermediate cells. X 70.

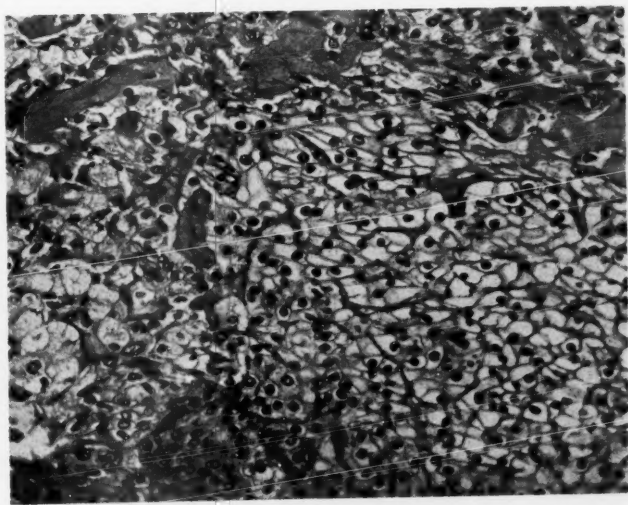


Fig. 6 (Case 2) A portion of a neoplasm formed principally of large, pale, polyhedral cells of hypernephroid appearance; little stroma. X 200.

after operation but three were between seven and ten years. Stewart et al. reported two similar late recurrences. One of the four cases with recurrence in our own series of 12 showed reappearance of tumor in eight years after excision and radiation. Recurrence of the others ranged from 6 to 20 months.

Regional lymph node metastases were found in 10 of the 45 cases reported by Stewart et al.² and represent a common feature in the more rapidly growing neoplasms. Kirklin et al.⁹ found metastasis to the regional nodes in 10.6 per cent. Three of the ten parotid tumors reported here revealed lymph node involvement and in a fourth, there was diffuse infiltration of the entire auriculo-parotid area.

Distant metastases were present in only 4 of the 45 cases in the series of Stewart et al.,² occurring in subcutaneous tissue, lungs, myocardium, liver and distant lymph nodes. McIntyre¹⁴ reported a fatal case of mucoepidermoid carcinoma of the tongue, of only eight months' duration and at autopsy showing massive local extension, and metastases to the pericardium, myocardium, omentum and mesentery, liver and adrenal. In the majority of instances, however, the neoplasm does not lead to the death of the patient.

Kirklin et al. traced 18 of 19 patients and reported a three year survival of 94.4 per cent, a five year survival of 83.3 per cent, and no further deaths. In the series of 12 presented here only one patient has died.

TREATMENT

Treatment consists of wide local excision. Allowance must be made for the fact that the gross margins are indistinct because of the common locally invasive nature of the tumor. Radiation therapy has been employed in a number of cases but its effectiveness cannot be evaluated with certainty. In our own series resection accompanied radiation in each instance where the latter was employed, making accurate evaluation of radiation therapy impossible. In one instance (case 9) radiation, 4800 r, was given without effect on the tumor, either in regard to size or histologic change as evidenced in the tissue removed two months later. However, after partial excision and interstitial radiation, the neoplasm clinically disappeared and has not been demonstrable for four years. In a second case (case 2), radiation given to a recurrence was stated as causing disappearance of the tumor, but there was recurrence in six months. In three other instances radiation did not prevent recurrence of the neoplasm.

MALIGNANCY

From the foregoing descriptions it seems evident that this salivary gland tumor should be regarded as a malignant neoplasm. Kirklin et al.⁹ were unable to find characteristics to separate them into benign and malignant groups and regarded them all as carcinoma. However, Rawson et al.⁸ found that the tumors of a higher grade malignancy had a low stroma-epithelium ratio. Cyst formation

is less common in those with greater malignancy. This is true in the one fatal case of our series (case 2). In the majority of instances the squamous component of the neoplasm is similar to non-keratinizing squamous cell carcinoma, and in biopsy material may be mistaken for this. Clear cells may be readily confused with carcinoma of renal origin. The characteristics of local invasion and repeated rapid recurrences would seem to indicate that this neoplasm should be classified as carcinoma, though generally of low grade malignancy.

Report of Cases

Ten of the 12 cases in this series arose in the parotid gland, one tumor arose in the hard palate and one in the base of the tongue. Certain features of the entire group are summarized in Table 2.

The combined occurrence of malignant mixed tumor and mucoepidermoid carcinoma was an unusual feature in case 5. Both elements were evident in parotid lymph nodes. The tumor on repeated recurrence, however, was purely mucoepidermoid.

A needle biopsy of the tumor of case 2 led at first to an erroneous diagnosis of squamous cell carcinoma. Limited biopsies of these neoplasms offer such a source of error since they may not include mucous elements and hence not be fully representative of the lesion. Clear cell areas may be confused with hypernephroma and, as might be expected, also might suggest sebaceous gland derivation.

The tumor in the one fatal case (case 2), though it was similar to the others in many regions, was in part poorly differentiated and showed nuclear variability, mitoses, irregular arrangement of epithelial elements, little stroma and a preponderance of the squamous and hypernephroid cell types (fig. 6).

SUMMARY

Twelve cases of mucoepidermoid carcinoma have been summarized and include ten from the parotid, one from the base of the tongue and one from the hard palate.

The pathologic features of the neoplasm are distinctive. It appears grossly as an invasive or at times circumscribed, partly cystic, pale gray mass, and is distinguished microscopically by the presence of several types of cells, principal among which are squamous epithelial cells and mucin-containing cells.

The clinical course of mucoepidermoid carcinoma is characterized by the initial appearance of a tumor mass, usually painless, slow growth, local invasiveness and local recurrences following excision. Although distant metastases of this tumor are uncommon, both the clinical features and the pathologic characteristics indicate that it should be regarded as malignant.

TABLE 2.
Summary of Cases

Case No.	Race Sex	Age Years	Site	Initial Symptoms	Pathologic Aspects	Therapy and Clinical Course
1	W F	44	Parotid	Swelling, 6 mo., slight pain.	Infiltrating. Well differentiated	Excision, radiation (2000 r); recurrence 6 mo., excision and radiation (1092 mc. hr.). Living without recurrence 6 yrs.
2	N F	25	Parotid	Swelling, postauricular. Few months.	Infiltrating, auricular canal, mastoid zygoma, parotid area. Poorly differentiated, cellular for most part.	Excision, recurrence 1 yr.; radiation, "24 treatments," disappearance of tumor; recurrence 6 mo.; biopsy 1 yr., fistula formation; radical excision 1 yr.; recurrence, cervical metastases, death 6 mo.
3	W F	52	Hard palate	Tumor, 8 yrs.	Infiltrating. Well differentiated.	Biopsy, contact radiation (4000 r); excision, coagulation. Living, no recurrence 1 yr.
4	W F	28	Parotid	Mass below left ear, 3 yrs.	Circumscribed, infiltrating, well differentiated. Metastasis to parotid lymph node.	Partial excision, interstitial radiation (1300 mc. hr.); recurrence 20 mo.; excision, interstitial radiation (1300 mc. hr.). Living 15 yrs.
5	W M	35	Parotid	Swelling, below right ear. Duration un-stated.	Mucoepidermoid tumor in mixed tumor. Metastases to periparotid lymph nodes. Recurrence as malignant mixed tumor and mucoepidermoid carcinoma, then as mucoepidermoid carcinoma only. Well differentiated.	Incision, "application of radium," recurrence 8 yrs., excision; recurrence, excision, 4 yrs.; prompt recurrence, excision 6 yrs.; recurrence 1 yr., excision; recurrence 4 yrs., excision. Living 7 years with small nodule in scar.
6	W F	56	Parotid	Swelling right side of face, 3 yrs.	Poorly defined. Well differentiated.	Radiation (1950 r), excision. Last seen 2 mo. after operation.

Table 2 (cont'd)

Case No.	Race Sex	Age Years	Site	Initial Symptoms	Pathologic Aspects	Therapy and Clinical Course
7	W F	41	Parotid	Swelling anterior to left ear, 4 yrs.	Encapsulated, grossly; microscopic invasion including adjoining lymph node. Moderately differentiated.	Excision, radiation (3100 r). Living without recurrence 7 yrs.
8	W F	31	Parotid	Enlarging mass behind right ear, 4 mo.	Infiltrating. Moderately differentiated.	Excision, radiation (3900 r). Living without recurrence, 26 mo.
9	W M	23	Parotid	Lump anterior to right ear, 2½ mo.	Infiltrating. Moderately differentiated.	Radiation (4800 r); partial excision in 2 mo., interstitial radiation. Living 4 yrs., no apparent neoplasm.
10	W M	52	Parotid	Tumor, anterior to left ear; fluctuating in size, 7 mo.	Grossly encapsulate, microscopic infiltration. Well differentiated.	Excision. Living 6 mo. no recurrence.
11	W F	32	Tongue	Cough; tumor found on physical examination	Infiltrating. Well differentiated basal and goblet cells.	Excision, cautery. Living 1 yr. no recurrence.
12	W F	62	Parotid	Lump at angle of left jaw, 3 yrs.	Infiltrating; mucous cysts, grossly.	Excision. Living 11 mo. no recurrence.

References

1. Schilling, F.: Beitrag zur Kenntnis der Parotisgeschwülste, Ziegler Beitrage z. path. Anat. **68**:139-160, 1921.
2. Volkmann, R.: Ueber endotheliale Geschwülste, zugleich ein Beitrag zu den Speicheldrüsen und Gaumentumoren. Deutsch Zeitschr. f. Chir., **41**:1-180, 1895.
3. Lecene, P.: Adenomes et Kystes della Parotide. Rev. de Chir. **37**:1-17, 1908.
4. Skorpil, R.: Ueber das schleimbildende Epitheliom der Speicheldrüsen. Virchow's Arch. f. Path. Anat. u. Physiol. **305**:661-794, 1940.
5. Stewart, F. W., Foote, F. W., and Becker, W. F.: Muco-epidermoid tumors of salivary glands. Ann. Surg. **122**:820-844 (Nov.) 1945.
6. Linell, F.: Mucus-secreting and cystic epidermoid carcinomas of mucous-and salivary glands. Acta path. et microbiol. Scandinav. **25**:801-828, 1948.
7. Godwin, J. T. and Colvin, S. H., Jr.: Benign mucoepidermoid tumor. Arch. Path. **47**:512-515 (May) 1949.
8. Rawson, A. J., Howard, J. M., Royster, H. P. and Horn, R. C., Jr.: Tumors of salivary glands; clinicopathologic study of 160 cases. Cancer **3**:445-458 (May) 1950.
9. Kirklin, J. W., McDonald, J. R., Harrington, S. W. and New, G. B.: Parotid tumors; histopathology, clinical behavior, and end results. Surg., Gynec. & Obst. **92**:721-733 (June) 1951.
10. Pung, S.: Muco-epidermoid tumor of the parotid gland. Report of case. Am. J. Clin. Path. **22**:1153-1156 (Dec.) 1952.
11. Bauer, W. H. and Bauer, J. D.: Classification of glandular tumors of salivary glands; study of 143 cases. Arch. Path. **55**:328-346 (April) 1953.
12. Slaughter, D. P., Southwick, H. W., and Walter, L.: The fate of recurrent or persistent parotid tumors. Surg., Gynec. & Obst. **96**:535-540 (May) 1953.
13. Owens, H.: Minor salivary gland tumors in respiratory tract and ear; review of literature and report of 2 cases. Laryngoscope **59**:960-983 (Sept.) 1949.
14. McIntyre, H. W.: Mucoepidermoid carcinoma of the salivary gland. Report of a case with autopsy findings. Arch. Path. **56**:79-83 (July) 1953.

EQUIPMENT FOR SAFE HANDLING OF RADIOACTIVE ISOTOPES

OTTO GLASSER, PH.D. and BERNARD TAUTKINS
Department of Biophysics

THE use of radioactive isotopes in medical institutions is growing continuously. Shipments of radioactive isotopes for medical therapy from the Oak Ridge National Laboratory have increased from approximately 500 in 1947 to 5000 in 1952. Proper protection against undesirable radiation of all those handling radioactive materials is of utmost importance and numerous articles and books on "health physics" are available.¹

Many pieces of safety equipment for handling radioactive isotopes are commercially available. They comprise lead and iron bricks (regular or interlocking), lead and iron storage containers, mobile lead safety shields and carriers, lead test tube racks, remote handling tongs and remote pipetting devices. Yet many isotope laboratories are confronted with individual protection problems which cannot always be solved with equipment on the market. Most commercial equipment is also expensive, and not all laboratories can afford this expense in addition to the fundamentally necessary instruments such as Geiger counters and monitors.

For these reasons we have constructed during the last few years several pieces of safety equipment which have proved useful. Although some of these pieces seem to be novel, no originality is claimed for any of the units described. These units are used in the Clinical Isotope Section at the Cleveland Clinic where the two isotopes, I^{131} and P^{32} , are used almost exclusively.

Isotope Storage Unit. A convenient storage arrangement can be set up with 2 by 4 by 8 inch lead bricks, which form the body of the unit, and 2 by 4 by 4 inch bricks for the top cover, as illustrated in the photograph and schematic drawing in figure 1. We were fortunate to inherit tons of lead from an old x-ray therapy department which was dismantled and the bricks were cast in our mechanical department. As can be seen in the photograph, they are left in the rough, except for those surfaces upon which the top cover bricks slide which are machined. Holes (diameter $1\frac{5}{8}$ inches, depth $3\frac{1}{8}$ inches) are drilled off-center in the middle layer of bricks to hold the bottles containing radioactive isotopes. Their position is so arranged that the radiation hits the places where the bricks touch obliquely, thus avoiding the necessity of using interlocking bricks. In the setup in figure 1 there are six numbered holes (only one is evident); five can be occupied leaving one space open to move the cover bricks. (Two of the cover bricks have been removed in the photograph to give a clearer view of the construction.) This storage unit is simple, cheap and flexible. It can be easily extended if more storage space is needed. It also can be easily dismantled and de-contamination is no problem.

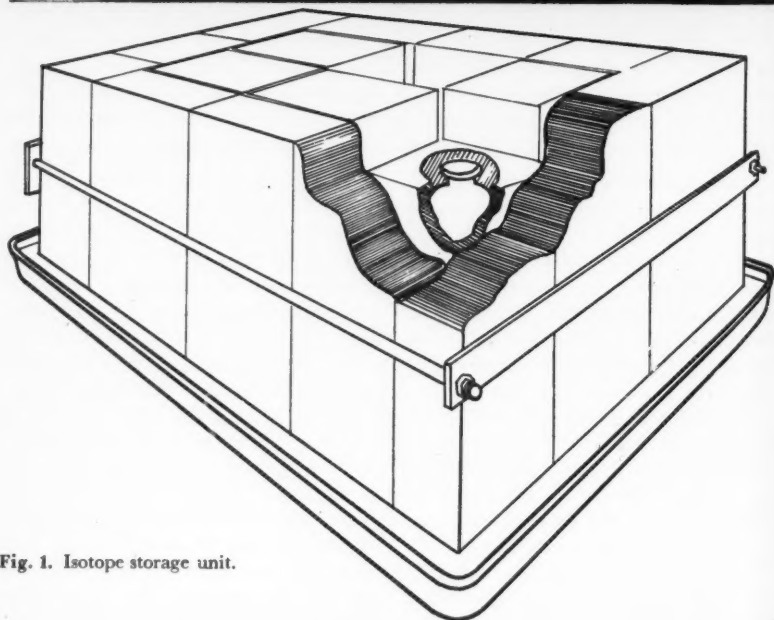


Fig. 1. Isotope storage unit.

RADIOACTIVE ISOTOPES

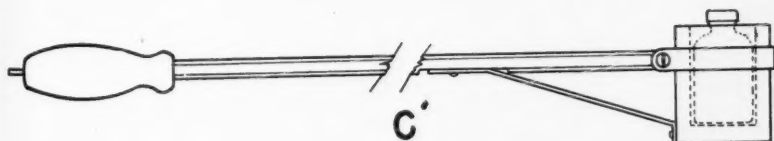
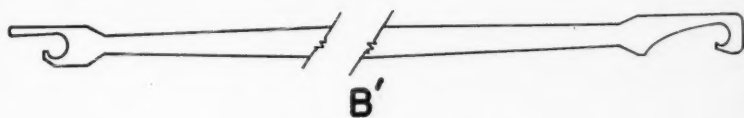
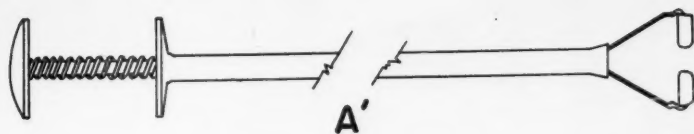
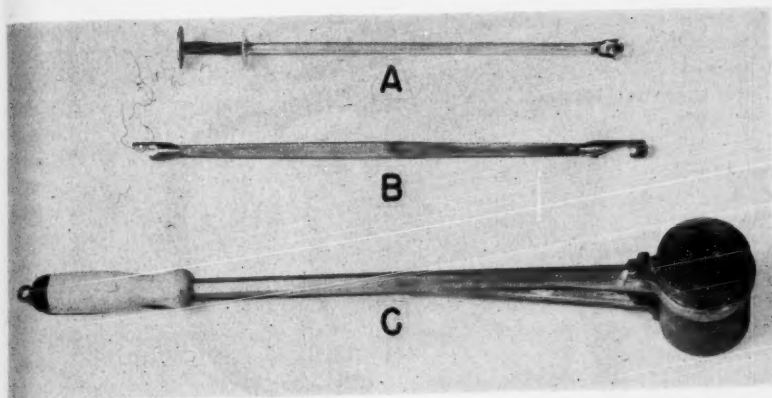


Fig. 2. Bottle cap remover and isotope carrier.

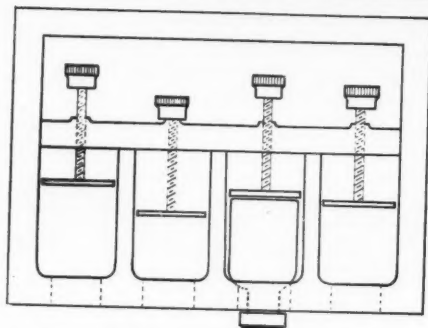
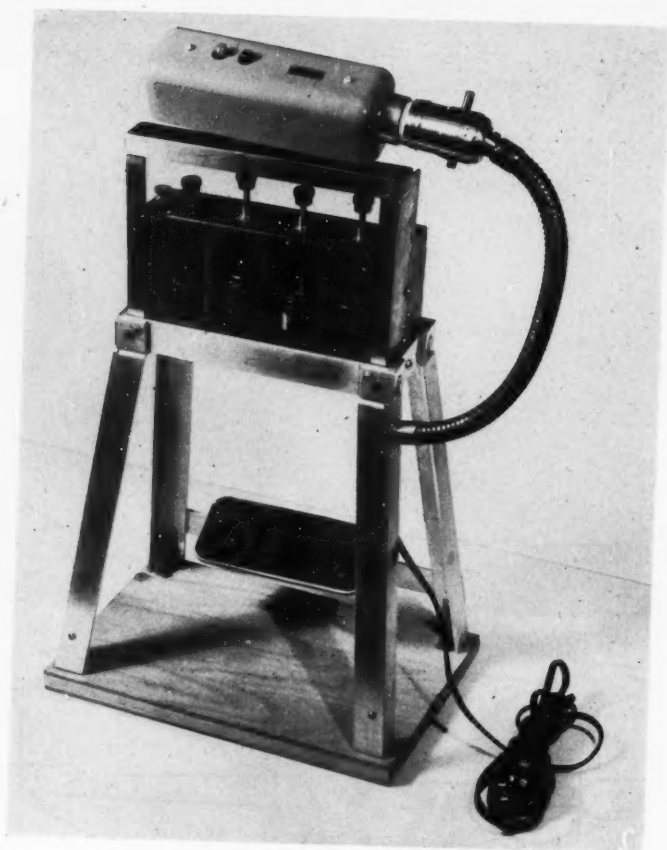


Fig. 3. Intravenous tracer bottle holder.

Bottle Cap Remover. Bottles with radioactive isotopes from Oak Ridge National Laboratory have screw caps, and returnable shipping containers are equipped with a bottle cap remover which permits easy removal of the cap. Sterile isotope solutions from pharmaceutical firms however come equipped with rubber stoppers and aluminum seals. These are difficult to open safely with ordinary laboratory tools. In order to overcome this difficulty we constructed the tools illustrated in the photograph and schematic drawings of figure 2. Figure 2 A and A¹ is a pick-up (length $12\frac{7}{8}$ inches) for the isotope bottle. Upon pressure on the button at one end, tongs with semicircular ends spread at the other end. They grasp the neck of the bottle and permit safe transfer to the lead carrier (length of handle $18\frac{1}{2}$ inches, lead thickness $\frac{7}{16}$ inch) illustrated in figure 2 C¹. The neck of the bottle protrudes above the upper edge of the container and permits easy removal of the rubber stopper and aluminum seal by means of either end of the bottle cap remover (fig. 2 B, B¹). For bottles with smaller diameters than illustrated, sleeves can be inserted into the lead carrier in order to hold the bottle tightly for cap removal. Both tongs and lead carrier lend themselves to many other uses in the isotope laboratory.

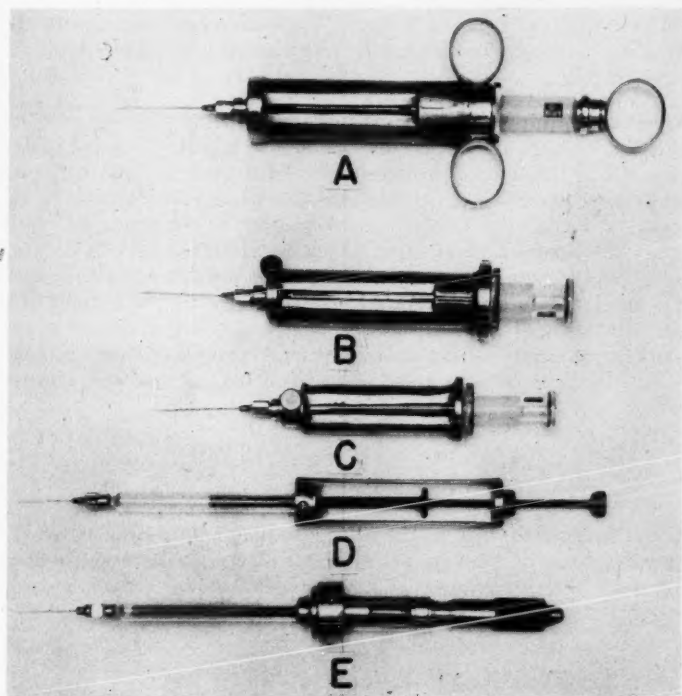


Fig. 4. Isotope syringes.

Intravenous Tracer Bottle Holder. The tracer bottle holder illustrated in figure 3, photograph and schematic drawing, has proved useful in the laboratory where large numbers of sterile isotope tracers are required. It consists of four lead protected partitions (2 by 4 by 8 inches) which hold four bottles. The bottles are placed upside down with the neck protruding through holes in the bottom lead plate and they are held in place by screw adjusters manipulated from the top. The front of the lead housing consists of a lead glass window 1 inch in thickness which permits a full view of the bottles and liquids and any manipulations therein. At the bottom of the stand is an adjustable automobile mirror which allows easy view of the rubber stoppers of the isotope bottles for insertion of the syringe needle. A fluorescent light furnishes adequate illumination for this procedure.

Isotope Syringes We have observed that syringes with lead shields of 5mm. thickness, as illustrated in figure 4 A, B, and C, permit quick loading and quick injection without being too bulky and heavy. The time of handling is thereby cut down to such an extent that the total exposure often is considerably below that of handling cumbersome syringes, notably when inserting the needle in the vein. Syringe D in figure 4 has an adjustable stop for the plunger which once set permits rapid metering of equal dosages for experimental work. Syringe 4E has a micrometer adjustment with which small amounts of liquid can be accurately expelled.

Disposable Equipment. In our Clinical Isotope Section where about 300 individual procedures are carried out per month, 100 of which are application of tracer doses, 120 uptake measurements, 40 treatments, and various other laboratory procedures, it is imperative that as much as possible of the equipment used to hold radioactive isotopes be disposable. Patients drink tracer and treatment isotopes from paper cups. Urine for clearance rates is measured in calibrated paper graduates or cups and the dipping counter for such measurements is covered with a thin readily available plastic test tube which after the measurement is disposed of with the paper cups. Using paper and plastics for such work has reduced to a minimum the disagreeable cleaning of contaminated glassware and the expense of these materials is far less than the gain in time and safety.

Conclusion

Several instruments and methods for safe handling of radioactive isotopes are discussed. Most of them are not available on the market and are described to aid those in the ever growing group of people handling radioactive isotopes.

Reference

1. e.g. Safe Handling of Radioactive Isotopes. Handbook 42, Department of Commerce, National Bureau of Standards, Washington, 1949.

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF

CRILE, G., JR. and GROVES, L. K.: Massive Leiomyosarcomas of stomach. *Gastroenterology* **24**:560-568 (Aug.) 1953.

CRILE, G., JR. and HAZARD, J. B.: Relationship of age of patient to natural history and prognosis of carcinoma of thyroid. *Ann. Surg.* **138**:33-38 (July) 1953.

CRILE, G., JR. and PERRYMAN, R. G.: Parathyroid cysts. *Surgery* **34**:151-154 (July) 1953.

DINSMORE, R. S.: Trends of surgery in the last decade. *Ann. Surg.* **138**:289-296 (Sept.) 1953.

GARDNER, W. J.: Neurosurgical clinic. *Postgrad. Med.* **13**:417-422 (May) 1953.

HIGGINS, C. C. and ARBER, F. W.: Malignant tumours of testicle. *Canad. M.A.J.* **69**:124-131 (Aug.) 1953.

KARNOSH, L. J.: Aphasia—etiology and classification. *Postgrad. Med.* **14**:118-120 (Aug.) 1953.

KARNOSH, L. J. (with the collaboration of Mereness, Dorothy): *Psychiatry for Nurses*, ed. 4, St. Louis, C. V. Mosby Co., 1953, pp.516.

KOLFF, W. J.: Treatment of uremia with forced high calorie-low protein diet. *Nutrition Reviews* **11**:193-196 (July) 1953.

McCULLAGH, E. P. and ZWICKEL, R. E.: Value of routine blood sugar tests in detection of diabetes mellitus. *J.A.M.A.* **152**:1031-1033 (July 11) 1953.

MASSON, G. M. C., DEL GRECO, F., CORCORAN, A. C. and PAGE, I. H.: Acute diffuse vascular disease elicited by renin in rats pretreated with cortisone. *A.M.A. Arch. Path.* **56**:23-35 (July) 1953.

MASSON, G. M. C., DEL GRECO, F., CORCORAN, A. C. and PAGE, I. H.: Factors influencing renin diuresis and proteinuria. *Proc. Soc. Exper. Biol. & Med.* **83**:631-636 (July) 1953.

PAGE, I. H. and McCUBBIN, J. W.: Renal vascular and systemic arterial pressure responses to nervous and chemical stimulation of kidney. *Am. J. Physiol.* **173**:411-420 (June) 1953.

PAGE, I. H. and McCUBBIN, J. W.: Variable arterial pressure response to serotonin in laboratory animals and man. *Circulation Research* **1**:354-362 (July) 1953.

POUTASSE, E. F. and HIGGINS, C. C.: Adrenal surgery for Cushing's syndrome. *J. Urol.* **70**:129-136 (Aug.) 1953.

ANNOUNCEMENTS

Physician-in-Chief Pro Tempore

Dr. Cecil J. Watson, professor of medicine, University of Minnesota, will be the third annual Physician-in-Chief pro tempore on December 17, 18 and 19, 1953. During his tenure, Dr. Watson will devote his entire time to the teaching program of the Fellows in Medicine. A schedule of daily clinics, lectures, and seminars has been arranged. Members of the medical profession are cordially invited to attend.

Saturday Morning Teaching Program

Members of the medical profession are cordially invited to attend the regular Saturday morning teaching program scheduled to begin September 12, 1953. The meetings take place on the 4th floor of the North Clinic Building and are scheduled as follows:

- | | |
|------------------|--|
| 8:00— 9:00 a.m. | Medical and Surgical Pathology Conferences and Specialty Seminars |
| 9:00—10:30 a.m. | Combined Medical and Surgical Clinical Conference—Presentation and Discussion of Interesting Cases |
| 10:40—11:30 a.m. | Medical Basic Science Seminar
Surgical Seminar |

Details of these weekly meetings may be obtained by contacting the Educational Secretary, The Bunts Institute, 2020 East 93rd Street, Cleveland, Ohio, or calling CEdar 1-6800.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

*Announces the following Postgraduate Continuation Course for
October 28 and 29, 1953*

REFRESHER COURSE IN GENERAL SURGERY

Tentative Program

Wednesday, October 28

Morning Session

R. S. DINSMORE, M.D., Presiding

8:30- 9:00 a.m. . Registration

9:00- 9:05 a.m. . Opening Remarks R. S. DINSMORE, M.D.

Thyroid Disease

9:05- 9:25 a.m. . Trends in Thyroid Surgery R. S. DINSMORE, M.D.

9:25- 9:55 a.m. . The Present-Day Therapy of
Hyperthyroidism E. P. McCULLAGH, M.D.

9:55-10:15 a.m. . Tumors of the Thyroid and Thyroiditis . . . GEORGE CRILE, JR., M.D.
J. B. HAZARD, M.D.

10:15-10:35 a.m. . Intermission

Surgery of Heart and Lungs

10:35-10:55 a.m. . Selection of Patients for Mitral
Commissurotomy A. C. ERNSTENE, M.D.

10:55-11:15 a.m. . Surgical Aspects of Mitral Commissurotomy . . . D. B. EFFLER, M.D.

11:15-11:35 a.m. . Indications for Lung Biopsy and Pulmonary
Exploration H. S. VAN ORDSTRAND, M.D.

11:35-11:55 a.m. . Selection of Patients for Surgery of Cardiac
Anomalies F. M. SONES, JR., M.D.

11:55-12:15 p.m. . Special Problems in Anesthesia for Operations upon
Heart and Lungs C. E. WASMUTH, M.D.

12:30 p.m. . . . Luncheon—Courtesy Bunts Institute

Afternoon Session

R. B. TURNBULL, JR., M.D., Presiding

Diseases of Biliary Tract and Pancreas

- 1:30- 1:45 p.m. . Indications for Surgery of the Gallbladder . . . R. S. DINSMORE, M.D.
1:45- 2:00 p.m. . Surgery of the Pancreas . . . S. O. HOERR, M.D.
2:00- 2:15 p.m. . Problems in Cholelithiasis . . . A. H. ROBNETT, M.D.
2:15- 2:30 p.m. . Hepatitis and Liver Biopsy . . . H. R. ROSSMILLER, M.D.

Diseases of Esophagus, Stomach, and Duodenum

- 2:30- 3:00 p.m. . Cancer of Upper Third of
Esophagus . . . EUGENE M. BRICKER, M.D. (Guest)*
3:00- 3:20 p.m. . Hiatus Hernia . . . D. B. EFFLER, M.D.
3:20- 3:30 p.m. . Intermission
3:30- 4:30 p.m. . Panel Discussion . . . S. O. HOERR, M.D. (Moderator)
E. M. BRICKER, M.D.*
GEORGE CRILE, JR., M.D.
C. H. BROWN, M.D.
5:30 p.m. . . . Dinner—Courtesy Bunts Institute
7:00 p.m. . . . Evening Lecture—Considerations of Extended Surgery for
Abdominal and Pelvic Cancer . . . E. M. BRICKER, M.D.*

Thursday, October 29

Morning Session

S. O. HOERR, M.D., Presiding

Miscellaneous Problems

- 9:00- 9:25 a.m. . Cancer of the Cervix . . . J. S. KRIEGER, M.D.
9:25- 9:50 a.m. . Hormone Therapy for Cancer . . . J. R. COOK, M.D.
9:50-10:15 a.m. . The Discharging Nipple . . . A. H. ROBNETT, M.D.
10:15-10:35 a.m. . Intermission
10:35-11:00 a.m. . The Injured Hand . . . G. S. PHALEN, M.D.
11:00-11:25 a.m. . Indications for Adrenalectomy . . . E. F. POUTASSE, M.D.
11:25-12:00 noon . What's New in Neurosurgery . . . W. J. GARDNER, M.D.
12:15 p.m. . . . Luncheon—Courtesy Bunts Institute

Afternoon Session

GEORGE CRILE, JR., M.D., Presiding

1:30- 3:00 p.m. . Panel Discussion—Diseases of Small

Intestine and Colon.GEORGE CRILE, JR., M.D. (Moderator)

E. M. BRICKER, M.D.*

R. B. TURNBULL, JR., M.D.

E. N. COLLINS, M.D.

L. J. MCCORMACK, M.D.

3:00- 3:10 p.m. . Intermission

3:10- 4:30 p.m. . Panel Discussion—Peripheral Vascular

DiseaseF. A. LEFEVRE, M.D. (Moderator)

V. G. DEWOLFE, M.D.

A. W. HUMPHRIES, M.D.

W. J. GARDNER, M.D.

A. H. ROBNETT, M.D.

* Guest Speaker:

Eugene M. Bricker, M.D.—Associate Professor of Surgery, Washington University
School of Medicine, St. Louis, Missouri.

REGISTRATION BLANK

EDUCATIONAL SECRETARY

THE FRANK E. BUNTS INSTITUTE

Cleveland Clinic

East 93rd Street and Euclid Avenue

Cleveland 6, Ohio

Please register me for the "Refresher Course in General Surgery" to be given October 28 and 29, 1953. (Registration Fee is \$15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for \$5.00 and the remainder will be paid on registration, October 28.

Checks should be made

payable to the Frank E.

Bunts Institute.

Name

Address

Medical School and

Date of Graduation

This course is open only to graduates of approved medical schools.

C
Alexa
ar
42
Ande

Ballin
Brow
ch
p
-, K
C
ac

Corce

deWo
L

Effler
m
- : s

Foc,

Gard
of
w
Glass
-, a
h

Harr
Harr
Harr
A

Hawl
m
Haza
G
Hells

ne
is

Hewl
to
th

Higg
tr
Hum
V

Kane
Kazd

INDEX

CLEVELAND CLINIC QUARTERLY—Volume 20—1953

AUTHOR INDEX

- Alexander, R. L. and Kennedy, R. J.: Lens in anterior chamber of eye: surgical removal, 437
- Anderson, Robin: Pedicled skin flap, 327
- Ballinger, C. S.: *see* Sones, F. M., Jr.
- Brown, C. H.: Further experience with anticholinergic drugs: clinical appraisal in 201 patients, 415
- , Kane, C. F. and Harrington, V. A., Jr.: Changes in surgery for carcinoma of stomach, 276
- Corcoran, A. C.: St. Luke, physician, 301
- deWolfe, V. G.: *see* Humphries, A. W.; *see* LeFevre, F. A.
- Effler, D. B.: Pectus excavatum: surgical treatment, 353
- : *see* Sones, F. M., Jr.
- Foe, Adrian: *see* Lovshin, L. L.
- Gardner, W. J. and Pinto, J. P.: Taarnhoj operation: relief of trigeminal neuralgia without numbness, 364
- Glasser, Otto: Human side of science, 400
- , and Tautkins, Bernard: Equipment for safe handling of radioactive isotopes, 457
- Harrington, V. A., Jr.: *see* Brown, C. H.
- Harris, H. E.: *see* Krech, W. J.
- Harrison, M. T. and Mercer, R. D.: Vitamin A intoxication, 424
- Hawk, W. A. and Hazard, J. B.: Factors in mechanism of metastasis: review, 389
- Hazard, J. B.: *see* Hawk, W. A.; *see* Stevenson, G. F.
- Hellstrom, John: Observations regarding prognosis and diagnosis of hyperparathyroidism, 253
- Hewlett, J. S. and Scott, Thornton: Responses to corticotropin (ACTH) and cortisone in thrombocytopenic states, 430
- Higgins, C. C. and Stearns, E. E.: Endometriosis of bladder; report of three cases, 333
- Humphries, A. W., LeFevre, F. A. and deWolfe, V. G.: Popliteal aneurysm, 247
- Kane, C. F.: *see* Brown, C. H.
- Kazdan, Philip: *see* Kennedy, R. J.
- Kennedy, R. J. and Kazdan, Philip: End results in retinal detachment surgery, 441
- : *see* Alexander, R. L.
- King, J. W.: Importance of fecal examination in diagnosis of strongyloidiasis, 359
- Krech, W. J. and Harris, H. E.: Resistant cases of Meniere's disease, 292
- LeFevre, F. A., Phalen, G. S. and deWolfe, V. G.: Intermittent claudication of hip, 375
- : *see* Humphries, A. W.
- Lovshin, L. L. and Foe, Adrian: Value of air encephalography and cerebral arteriography in diagnosis of headache, 394
- McCormack, L. J.: *see* Turnbull, R. B., Jr.
- Mercer, R. D.: *see* Harrison, M. T.
- Nelson, P. A.: Therapeutic basis of breathing exercises, 269
- Phalen, G. S.: *see* LeFevre, F. A.
- Pinto, J. P.: *see* Gardner, W. J.
- Poutasse, E. F.: Prostate gland biopsy, 263
- Scott, Thornton: *see* Hewlett, J. S.
- Skillern, Penn G.: Etiology, diagnosis and treatment of thyroid failure, 317
- Sones, F. M., Jr., Effler, D. B. and Ballinger, C. S.: Surgery for mitral stenosis, 237
- Stearns, E. E.: *see* Higgins, C. C.
- Stevenson, G. F. and Hazard, J. B.: Mucoepidermoid carcinoma of salivary gland origin, 445
- Strittmatter, W. C. and Wise, R. E.: Roentgenologic diagnosis of jejunal or marginal ulcer, 286
- Tautkins, Bernard: *see* Glasser, Otto
- Tingwald, F. R.: Polyps of digestive pharynx, 397
- Turnbull, R. B., Jr. and McCormack, L. J.: Reoperated congenital megacolon, 339
- : *see* Wasmuth, C. E.
- Wasmuth, C. E.: Anesthesia for mitral commissurotomy, 346
- : Pentothal anesthesia in infants and children, 381
- and Turnbull, R. B., Jr.: Continuous spinal anesthesia in colon surgery, 257
- Wise, R. E.: *see* Strittmatter, W. C.

SUBJECT INDEX

Entries set in *italics* refer to specific article titles

- Anesthesia
 - continuous spinal, in colon surgery, 257
 - pentothal, use of in infants and children, 381
- Anesthesia for mitral commissurotomy*, 346
- Aneurysm, popliteal, 247
- Announcements, 464
- Arteriography, cerebral, value of in diagnosis of headache, 394
- Biopsy, prostate gland, 263
- Bladder, endometriosis of, 333
- Bunts Institute Courses, tentative programs
 - current therapy in pediatric practice, 409
 - medical and surgical disorders of the urinary tract, 311
 - pathology and pathologic physiology in internal medicine, 307
 - postgraduate course of particular interest to general practitioners, 369
 - refresher course in general surgery, 465
- Carcinoma
 - mucocpidermoid, origin of in salivary gland, 445
 - of stomach, changes in surgery for, 276
- Changes in surgery for carcinoma of stomach*, 276
- Claudication, intermittent, of hip, 375
- Colon, continuous spinal anesthesia in surgery of, 257
- Commissurotomy, mitral, anesthesia for, 346
- Continuous spinal anesthesia in colon surgery*, 257
- Corticotropin, responses to in thrombocytopenic states, 430
- Cortisone, responses to in thrombocytopenic states, 430
- Drugs, anticholinergic, clinical appraisal of, 415
- Encephalography, air, value of in diagnosis of headache, 394
- End results in retinal detachment surgery*, 441
- Endometriosis of bladder: report of three cases*, 333
- Equipment for safe handling of radioactive isotopes*, 457
- Etiology, diagnosis and treatment of thyroid failure*, 317
- Exercises, breathing, therapeutic basis of, 269
- Eyes
 - lens in anterior chamber, surgical removal of, 437
 - retinal detachment, end results in surgery for, 441
- Factors in mechanism of metastasis: review*, 389
- Further experience with anticholinergic drugs: clinical appraisal in 201 patients*, 415
- Glands
 - prostate, biopsy of, 263
 - salivary, origin of mucocpidermoid carcinoma, 445
- Headache, diagnosis of, 394
- Hip, intermittent claudication of, 375
- History
 - Röntgen, W. C., 400
 - St. Luke, 301
- Human side of science*, 400
- Hyperparathyroidism, prognosis and diagnosis of, 253
- Importance of fecal examination in diagnosis of stronglyloidiasis*, 359
- Intermittent claudication of hip*, 375
- Intoxication, vitamin A, 424
- Isotopes, radioactive, safe handling of, equipment for, 457
- Lens in anterior chamber of eye: surgical removal*, 437
- Lower fellowship prize thesis, 292
- Megacolon, congenital, reoperated, 339
- Meniere's disease, resistant cases of, 292
- Metastasis, factors in, mechanism of, 389
- Mitral valve
 - commissurotomy, anesthesia for, 346
 - stenosis, surgery for, 237
- Mucocpidermoid carcinoma of salivary gland origin*, 445
- Neurological surgery, Taarnhoj operation, 364
- Observations regarding prognosis and diagnosis of hyperparathyroidism*, 253
- Pectus excavatum: surgical treatment*, 353
- Pedicled skin flap*, 327
- Pentothol anesthesia in infants and children*, 381
- Pharynx, digestive, polyps of, 397
- Plastic Surgery, 327
- Polyps of digestive pharynx*, 397
- Popliteal aneurysm*, 247
- Prostate gland biopsy*, 263
- Publications by staff, listings of, 305, 368, 407, 463
- Radioactive isotopes, safe handling of, equipment for, 457
- Reoperated congenital megacolon*, 339
- Resistant cases of Meniere's disease*, 292
- Responses to corticotropin (ACTH) and cortisone in thrombocytopenic states*, 430
- Roenigenologic diagnosis of jejunal or marginal ulcer*, 286
- Röntgen, W. C., character of, 400

SUBJECT INDEX - Continued

B. Luke, physician, 301

Stomach, changes in surgery for carcinoma of, 276

Strongyloidiasis, diagnosis of, 359

Surgery for mitral stenosis, 237

Taanhoj operation: relief of trigeminal neuralgia without numbness, 364

Therapeutic basis of breathing exercises, 269

Thrombocytopenia, corticotropin and cortisone responses in, 430

Thyroid, failure of, 317

Trigeminal neuralgia, operative relief of without numbness, 364

Ulcer, jejunal or marginal, roentgenologic diagnosis of, 286

Value of air encephalography and cerebral arteriography in diagnosis of headache, 394

Vitamin A intoxication, 424